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Enzymatically Asymmetrised Chiral Building Blocks for the Synthesis of Complex Natural Product Analogues: The Synthesis of Dynemicin Analogues from 2-(Quinolin-4-yl)propane-1,3-diol

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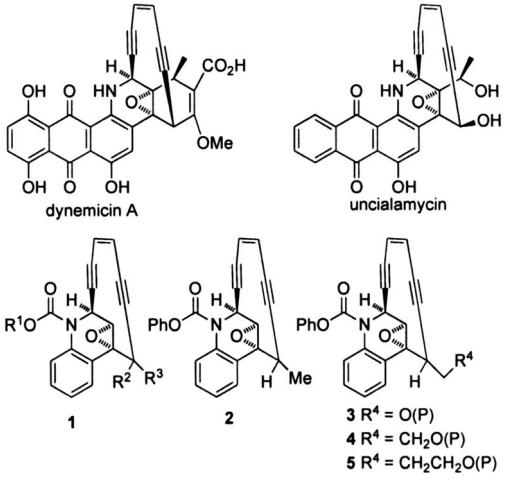
Full details of our synthetic approaches directed towards the enantioselective synthesis of new dynemicin analogues each containing a side-arm (a "handle") incorporating a protected alcohol are reported.

Introduction

Natural enediyne antibiotics are a small family of cyclic derivatives endowed with very interesting biological activities.[1–4] Their highly individual mode of action is due to Bergmann cycloaromatisation, generating a diradical that in turn brings about the cleavage of two complementary DNA strands. The most important enediynes are characterised by 10-membered 3-ene-1,5-diyne cyclic structures embedded in complex bridged polycyclic systems. They incorporate appropriate stabilizing moieties ("safety-locks"), which prevent the Bergmann cycloaromatisation occurring, and which are removed in vivo by appropriate "triggering" events. The most renowned and potent enediyne, calicheamycin γ_1^I, is currently in clinical use, under the brand name mylotarg®, as its conjugate with a humanised anti-CD33 antibody.

Other important natural products containing 10-membered 3-ene-1,5-diyne systems are dynemicin A[5] and uncialamycin[6,7] (Scheme 1), which share several common features. They are each characterised by the presence of an anthraquinone structure, a DNA-intercalating system typical of other very important anticancer agents. The stabilizing element ("safety-lock") is represented here by the epoxide, whereas the "trigger" is the quinone. Its bioreduction initiates a cascade of events culminating in the hydrolytic opening of the epoxide, followed by facile Bergmann cycloaromatisation, resulting in single and double cleavage of the DNA strands.



Scheme 1.

Dynemicin and uncialamycin, each lacking an oligosaccharide unit, are structurally simpler than chalicheamicin and for this reason have been deemed particularly well suited for the development of simplified analogues. First Nicolaou,[8–11] and then many others,[12–19] including our group,[20,21] have designed various derivatives corresponding to the general structure **1** (Scheme 1), which are often endowed with potent DNA-cleaving and/or cytotoxic activities. However, deletion of the naphthoquinone fragment calls for the development of a different type of trigger.[22] The observation that the epoxide is quickly hydrolysed when the tetrahydroquinoline nitrogen is free makes their urethane derivatives ideal stabilizing elements ("safety-locks"). The R^1 group must be suitably designed in order to allow cleavage of the carbamate under a variety of controlled conditions. Previous work has also shown that maximum activity is obtained when one of R^2 and R^3 is hydrogen and neither is an OH or OR group, as in the case of

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dynemicin, but in contrast to uncialamycin. This presents some limitations in the choice of the synthetic strategies, excluding – for example – cyclisation of the ten-membered ring through an intramolecular acetylide addition to a carbonyl group.

In a previous paper we reported a novel synthetic approach to the synthesis of both diastereomers of compounds **2**,[20] in which the two structural criteria quoted above are satisfied. One of the two diastereomers, after conversion into a β-sulfonylethyl carbamate, showed a very promising DNA-cleaving activity.[21]

However, that synthesis gave a racemic mixture. Although in most cases dynemicin analogues have been prepared as racemates, in two previous cases the synthesis of enantiomerically pure compounds has been reported.[23,24] Biological tests have indicated that the absolute configurations have an important influence on activity.

Moreover, because of the lack of suitable attaching points ("handles"), it was not possible to modulate the biological activity by joining DNA-complexing moieties as surrogates of the missing anthraquinone intercalating substructure. We[25] and others[1] have demonstrated that conjugation of simplified enediynes with DNA-intercalating agents or minor groove binders can enhance their DNA-cleaving efficiencies.

In order to overcome these limitations, an enantioselective synthesis of more complex analogues of **2**, possessing suitable attaching points, was designed. They are represented by general structures **3**, **4** or **5** (Scheme 2).

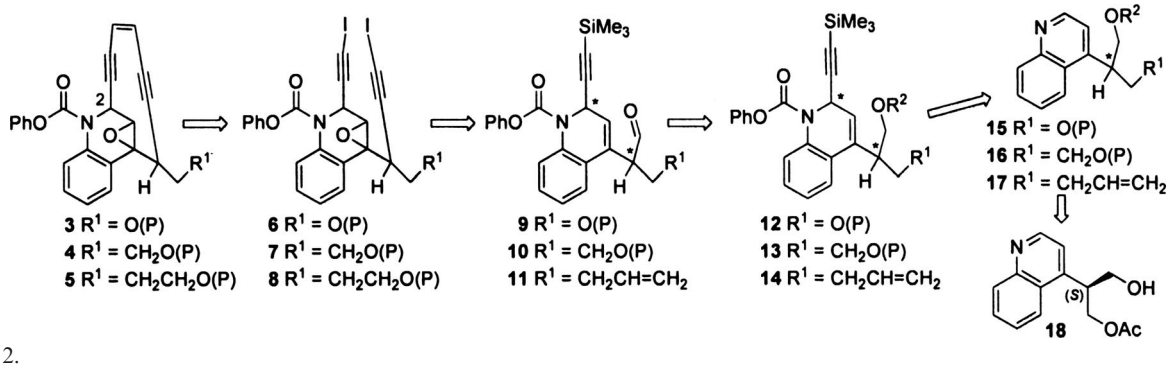
Results and Discussion

The retrosynthetic analysis is shown in Scheme 2, and entails, as key steps, the enzymatic asymmetrisation of prochiral 2-(quinolin-4-yl)propane-1,3-diol to give the monoacetate **18**,[26–35] the diastereoselective addition of trimethylsilyl acetylide to the quinolines **15**–**17**, the homologation of the aldehydes **9**–**11** to terminal alkynes, and finally the Danishefsky cyclisation[36] of the diiodoalkynes **6**–**8** under Stille conditions. This strategy would in principle allow the preparation of all four possible stereoisomers with respect to *C*-2 and to the stereogenic centre that bears the side arm,[37] and so stereochemical notations are deliberately omitted in Scheme 2.

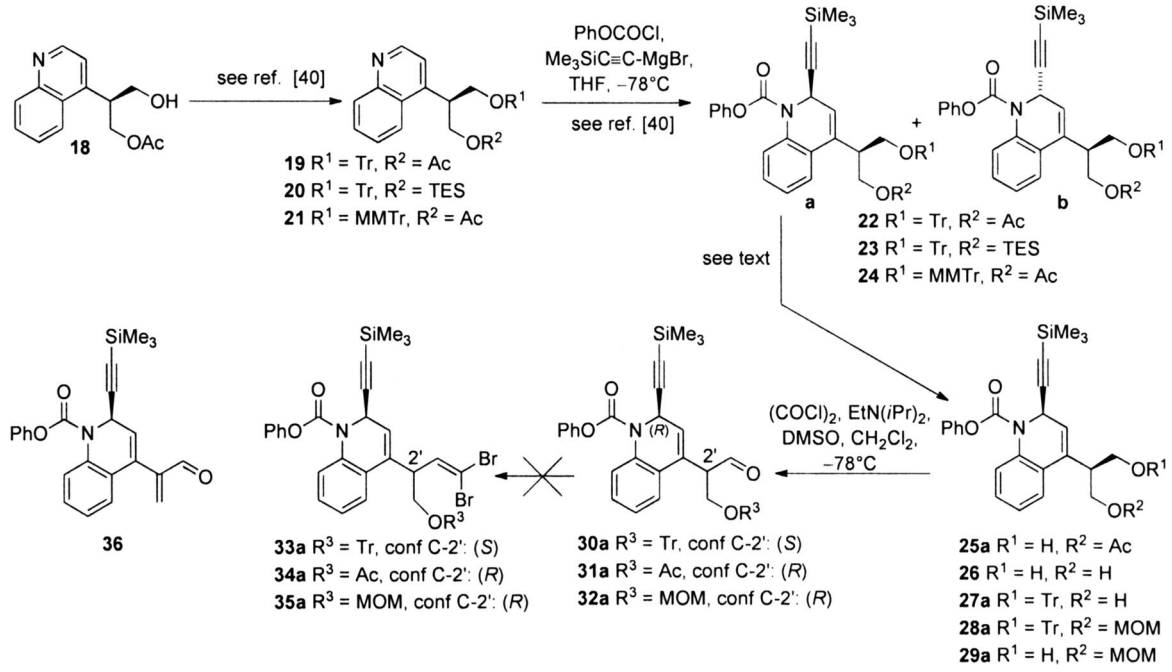
The success of this strategy, with the obtainment of a compound corresponding to formula **4**, had been already published in preliminary form.[38] Now we report the full description of our efforts, including the (unsuccessful) approach towards compounds **3** and **5** and the exploration of alternative routes for adducts **4**. A thorough survey of the influence of the protecting groups on the diastereoselectivity of the key acetylide addition to the quinoline nucleus is also provided.

We first studied the synthesis of compounds **3**, each containing a side arm with just one carbon atom (Scheme 3). To that end we started from (*S*)-**18**, the efficient and enantioselective synthesis of which (in 97% *ee*) had been already reported by us.[39] The monoacetate (*S*)-**18** was converted into the three orthogonally diprotected 2-(quinolin-4-yl)-propane-1,3-diols **19**–**21** (Scheme 3). In a previous work[40] we had already described the yields and diastereoselectivities of protecting-group-controlled Yamaguchi[41,42] additions of magnesium trimethylsilylacetylide to these derivatives. The best results were obtained with compound **19**, containing the triphenylmethyl (Tr) and acetyl groups, which gave a 94% yield with a 70:30 diastereomeric ratio. In that work we also found that it was not possible to use a quinoline bearing a free hydroxy group on one of the two side-arms, because of extensive decomposition during the addition reaction.[40]

The synthesis was therefore continued with the major adduct **22a**, after its chromatographic separation from **22b**. The first task was the selective monodeprotection of one of the two synthetically equivalent arms. The most obvious approach involves removal of the triphenylmethyl group. To our surprise, however, the usual conditions (*p*TSA in MeOH) furnished **25a** in only 28% yield, the main product being the diol **26** (61% yield). On switching to *i*PrOH the selectivity was even lower, the amount of diol increasing to 68%, whereas in *t*BuOH no reaction occurred. Solvolysis of an acetyl group under such mild conditions is rather uncommon, but intramolecular assistance from the other OH group is probably highly influential here. Milder protic acids did not give better results, but we eventually succeeded in obtaining **25a** in 80% yield by use of zinc bromide in CH_2Cl_2/*i*PrOH (85:15).[43] Because 50 equiv. of $ZnBr_2$ were required in order to drive the reaction to completion (owing to the existence of an equilibrium between the monoalcohol and the trityl ether), however, the reaction was not very



Scheme 2.



Scheme 3.

practical. Switching to a more labile trityl analogue [*p*-methoxyphenyl diphenylmethyl (MMTR)] was also not particularly successful, because of poor yields in the Yamaguchi addition leading to **24a**[40] and of poor selectivity in its monodeprotection.

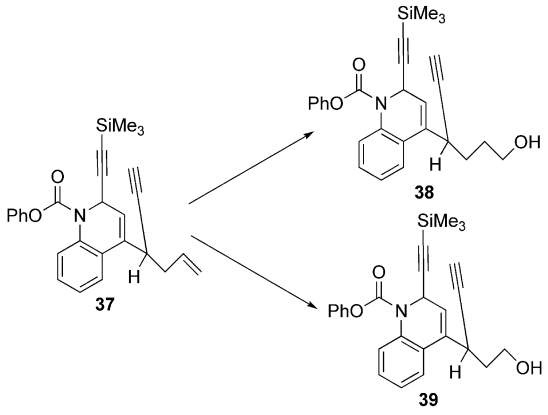
We therefore tried to remove the other protecting group in **22a** – the acetyl group – selectively. Conventional saponification with alkaline hydroxides was not possible because of concurrent removal of the trimethylsilyl group from the alkyne, which was in turn detrimental for the subsequent Corey–Fuchs protocol. We thus tried enzymatic hydrolysis with a series of lipases. None of them accepted **22a** as a substrate, with the exception of CAL (*Candida antarctica* lipase). However, even at 60 °C and after long reaction times, the reaction failed to reach completion, and the isolated yields of **27a** were never higher than 61%.

These unsatisfactory results prompted us to prepare another monoprotected derivative, compound **27a**, by starting from the Yamaguchi adduct **23a**, notwithstanding the slightly lower diastereoselectivity observed in its preparation (60:40 instead of 70:30).[40] The triethylsilyl group could be indeed selectively removed with HF at –18 °C in nearly quantitative yield to afford **27a**.

We also prepared the third alcohol **29a**, starting from **27a**, through reprotection of the free hydroxy group as the methoxymethyl ether (MOM) in 86% yield [MOM-Cl, $EtN(iPr)_2$, CH_2Cl_2, room temp.] followed by trityl cleavage (0.1 N HCl in MeOH, room temp., 68%).[44] This time we did not observe any formation of diol **26**.

Oxidation of these alcohols to the corresponding aldehydes is a delicate step, because of possible epimerisation. The best conditions were found to be the use of a modified Swern oxidation in the presence of Hünig's base [$EtN(iPr)_2$] at –78 °C. The workup conditions were also very important. A quick acid wash, in order to remove excess amine prior to concentration to dryness, was essential. These optimised conditions were always used by us throughout the work described in this paper. The aldehyde **30a** was found to be completely stable to epimerisation and could even be chromatographed without problems. Under the same oxidation conditions the aldehyde **31a** gave no epimerisation, but a 12% yield of the elimination product **36** was formed. Finally, the aldehyde **32a** represented the most critical case. The crude product consisted of a mixture of **32a**, its epimer **32b** and the elimination product **36** in a 62:18:20 ratio.

The subsequent Corey–Fuchs protocol,[45,46] for the generation of the necessary triple bond, was attempted first on the most stable aldehyde: compound **30a**. However, we never succeeded in obtaining the desired dibromide **33a**. As discussed in depth in the next section, this is probably the most crucial step of the whole synthetic sequence, because of the lability of the starting aldehydes, which are prone to epimerisation, elimination and rearomatisation processes. In particular, in the case of **30a**, unlike in our previous work,[21] the reaction did not take place at low temperature, whereas on increasing the temperature to room temp. extensive decomposition took place, affording mainly the elimination product **36**. Reasoning that the steric bulk of the trityl group could be responsible for this behaviour, we attempted the same protocol with the aldehydes **31a** and **32a**, but with similar results, showing that the problem is more electronic than steric: the β-alkoxy groups make these aldehydes less reactive and particularly sensitive to elimination/epimerisation reactions. Alternative methods[47,48] for the synthesis of terminal alkynes from these aldehydes also failed.

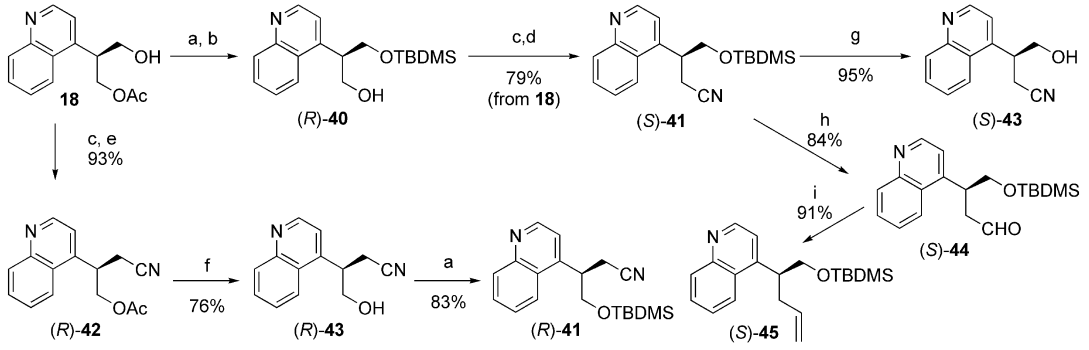


Scheme 4.

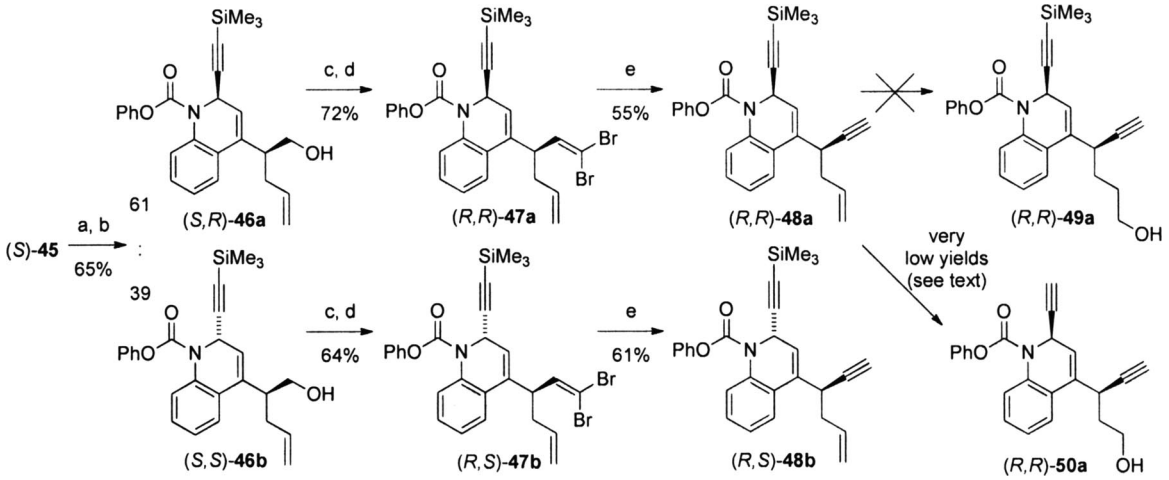
These unsatisfactory attempts prompted us to concentrate on the synthesis of compounds **4** and **5**, each characterised by a longer oxygenated side-arm (Scheme 2). We reasoned that the alkene **37** could be an useful advanced intermediate for both (Scheme 4). Compound **37** might in principle be transformed into the alcohol **38**, by hydroboration/oxidation, or be degraded into alcohol **39** through oxidative cleavage of the double bond followed by reduction. With a branched route we might therefore have access to two classes of simplified dynemicin analogues with side-arms of different lengths.

Scheme 5 shows the preparation of both enantiomers of the key silyl ether **41**. The potential to generate both enantiomers from a starting common intermediate is a typical property of asymmetrised 2-substituted propane-1,3-diols, stemming from their latent C_S symmetry. Homologation of one of the two side-arms was achieved by S_N2 substitution of a tosylate by cyanide ion. The two-step protocol (tosylation and substitution) worked without any problems with silyl ether **40** to afford (*S*)-**41** in high yields.[40] The reaction of the tosylate derived from the monoacetate **18**, on the other hand, was more tricky, being complicated by a concurrent elimination reaction, especially when working at 60 °C. Fortunately, when operating at room temp. this side reaction was nearly suppressed. The nitrile (*R*)-**42** was then converted into (*R*)-**41** by a high-yield protecting group interchange. The enantiomeric purities of (*S*)- or (*R*)-**43** were determined through formation of Mosher's esters and their examination by ^{1}H NMR (*ee* 96% for both).

The synthesis was continued with (*S*)-**41**. Reduction with DIBALH gave the aldehyde (*S*)-**44**, which was methylenated to give (*S*)-**45**. This last reaction was more troublesome than expected. Although various alternative literature



Scheme 5. *Reagents and conditions*: a) TBDMSCl, imidazole, DMF, room temp.; b) KOH, MeOH, 0 °C; c) TsCl, pyridine, room temp.; d) KCN, nBu$_4$NI, DMSO, 60 °C; e) KCN, nBu$_4$NI, DMSO, room temp.; f) MeONa (0.17 M), MeOH/THF, 0 °C, 80 min; g) HF, CH_3CN/H_2O, 0 °C; h) DIBALH, –70 °C; i) $[Ph_3PMe]Br$, $NaNH_2$, THF, –78 °C→0 °C.



Scheme 6. *Reagents and conditions*: a) PhOCOCl, $Me_3SiC{\equiv}CMgBr$, THF, –78 °C; b) HF, CH_3CN/H_2O, 0 °C; c) $(COCl)_2$, DMSO, $EtN(iPr)_2$, CH_2Cl_2, –78 °C; d) CBr_4, PPh_3, CH_2Cl_2, –78 °C→–40 °C; e) nBuLi, THF, –78 °C, 15 min.

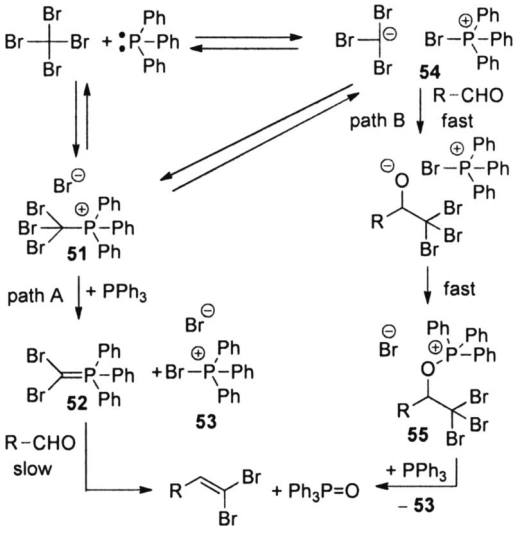
methods[49] failed, we obtained a good yield by the "instant ylide" method.[50,51] Yamaguchi addition to the quinoline (*S*)-**45** (Scheme 6) afforded rather low stereoselection in relation to previously studied chiral quinolines.[40] Moreover, the two diastereomers could be efficiently separated only after removal of the silyl ether, on compounds **46a** and **46b**.

The stage was set for another crucial transformation: oxidation to the aldehyde and conversion into a terminal alkyne by the Corey–Fuchs methodology, which was thoroughly explored with the major alcohol **46a**. Whereas oxidation under the modified Swern conditions described above worked this time uneventfully without any epimerisation, treatment with CBr_4 and PPh_3 turned out to be troublesome. The standard Corey–Fuchs conditions[45] involve pre-treatment of CBr_4 with PPh_3 (2 equiv.) to give a dibromomethylphosphorane, followed by addition of the aldehyde at 0 °C or room temp. Under these conditions, however, no desired product **47a** was obtained and the starting material was completely destroyed. The addition of buffering agents[46] such as Et_3N or 2,6-lutidine, as well as the use of zinc,[52] did not change the situation. If the preformed phosphorane was cooled to –78 °C and treated with the aldehyde, no reaction took place until the temperature was raised: only at –20 °C did the aldehyde start to react, but the desired product was also formed in low yield in this case, with extensive decomposition.

On the other hand, rapid addition of PPh_3 and CBr_4 to the cooled (–78 °C) aldehyde solution brought about the rapid, but incomplete, formation of the dibromide **47**. The reaction was poorly reproducible and in all cases tended to stop at various degrees of conversion: warming to –40 °C did not increase conversion, whereas warming to –20 °C or higher temperatures brought about decomposition not only of the starting material, but also of the product itself.

To the best of our knowledge, apart from a pioneering work by McKelvie,[53] no in-depth study on the mechanism of this useful transformation has been carried out. A literature search showed that this reaction was in most cases carried out at 0 °C or room temp. with reaction times from 30 min to 22 h,[54–63] whereas in other cases the same reaction was reported to take place in less than one hour at –78 °C.[64,65] This suggested two alternative pathways: one fast, taking place even at –78 °C, and another one slow, going through the phosphorane **52** (Scheme 7). Two papers seemed particularly interesting to us: Bestmann reported that better yields could be obtained by addition of CBr_4 to the mixture of aldehyde and PPh_3,[66] whereas Weinreb, in his total synthesis of licoricidin,[64] faced a situation similar to ours – under the classical conditions (high temperature) only aldehyde decomposition was observed, whereas, upon mixing all three reagents at –78 °C, a very fast reaction (only 5 min) gave the expected product in good yields. The same result could be also achieved by using a mixture of $CHBr_3$ and KO*t*Bu in the presence of PPh_3.

This latter evidence led us to propose the scenario shown in Scheme 7. Triphenylphosphane can react with CBr_4 in two different ways: nucleophilic attack at the carbon atom would give the intermediate **51**, whereas attack at a bromine



Scheme 7. Possible mechanism of the Corey–Fuchs reaction.

would generate the ionic pair **54**. Moreover, **51** could derive from **54** by phosphorus-centred nucleophilic substitution of bromine by Br_3C^-. It should be noted that ionic pairs such as **54** are universally considered the first products of interaction between PPh_3 and CBr_4 or CCl_4 and therefore the key intermediates of the Appel reaction.[67] However, these two alternative reactions are probably reversible. In the absence of an aldehyde (or of a proton source as in the Appel reaction), the equilibrium between **54** and **51** would soon be shifted towards the phosphorane **52** and the dibromide **53** by the irreversible reaction of **51** with a second molecule of PPh_3. The resulting phosphorane **52** would then react with an aldehyde through a "slow" Wittig mechanism to afford the final product (alkenyl dibromide). On the other hand, if an aldehyde were present from the beginning, the ionic pair **54** could react irreversibly with it to afford the intermediate **55**, which upon intervention of a second PPh_3 molecule would give the alkenyl dibromide, triphenylphosphane oxide and the dibromo triphenylphosphane **53**.

The existence of these alternative mechanisms is not usually an issue, because the "slow" path is convenient in most instances. In our case, however, the high lability of the dihydroquinoline system in the presence of an electrophilic reagent such as dibromotriphenylphosphane **53** makes only the "fast" mechanism productive.

Being confident that the scenario shown in Scheme 7 was correct, we reasoned that the "fast" mechanism would have been favoured by low temperature and by the presence of the aldehyde from the beginning, but also by a lower concentration of PPh_3. Actually, it is PPh_3 that promotes the first irreversible step of path A, whereas in path B the second molecule of PPh_3 is involved only at a later stage.

We thus treated the aldehyde at –78 °C with CBr_4 (2 equiv.) and then slowly added a solution of PPh_3 (3 equiv.) in dropwise fashion. The temperature was then allowed to rise to –40 °C (but not more!). We were pleased to find that under these conditions a good and reproducible yield of dibromides **47a** and **47b** could be obtained. We

think that these conditions may be useful in all those cases in which the traditional methodology fails.

The next elimination to afford the terminal alkynes **48a** and **48b** (Scheme 6) proceeded well, provided that exactly 2 equiv. of *n*BuLi were used at –78 °C, that the reaction was carried out under argon, and that it was quenched after 5–15 min. The presence of an excess of base or use of longer reaction times led to deprotonation of the relatively acidic proton at the *C*-2 position in the dihydroquinoline, resulting in fast aromatisation.

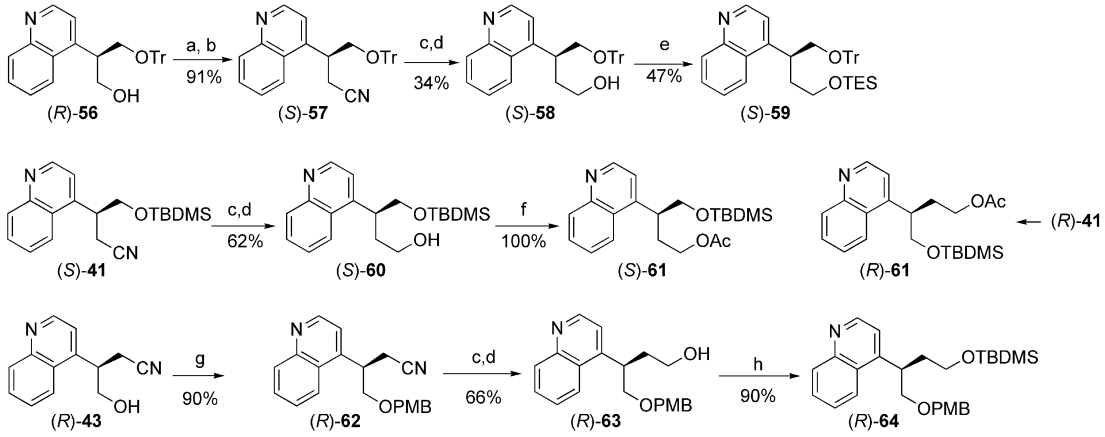
With dienediynes **48a** and **48b** to hand we studied the hydroboration reaction, hoping to form the desired alcohols **49**. We performed several experiments with the major isomer **48a**, but unfortunately, and surprisingly, we did not succeed in obtaining the desired product. All attempts to effect ozonolysis of the double bond also failed. On the other hand, a sequence of dihydroxylation of **48a** with OsO_4, followed by $NaIO_4$ treatment, led to the alcohol **50a**, with concurrent desilylation of the alkyne. The overall yield, however, was very low. Because we later succeeded in obtaining the same alcohol **50a** through a more efficient route (see below), this approach was abandoned.

The "allylic" route was mainly devised for the synthesis of the alcohols **49**, with longer arms, but the unexpected failure of all hydroboration attempts frustrated this design. However, the lessons learned during this approach, especially those relating to the Corey–Fuchs reaction, turned out to be crucial for the studies described next.

The obvious alternative synthesis of compounds **4** involves a Yamaguchi trimethylsilylacetylide addition onto a quinoline of general formula **16** (Scheme 2), with two side arms of different lengths (one and two carbon atoms), each bearing a protected alcohol. The choice of protecting groups was not trivial. They must be compatible with the Yamaguchi addition, and the one on the shorter arm must be selectively removable in the presence of the other. In addition, the one on the longer arm must be compatible with the Corey–Fuchs protocol and be removable smoothly at the end of the synthesis. Finally, in order to allow modulation of the stereoselectivity, they should have different electronic and steric properties. In order to evaluate these effects, and also to select the best combination of protecting groups, we prepared the three different diprotected systems **59**, **61** and **64** (Scheme 8). The nitrile (*S*)-**57** was obtained from the monoacetate **18** through conversion into (*R*)-**56**,[40] and subsequent homologation of the propane-1,3-diol system by the protocol described above (Scheme 5; replacement of a tosylate by cyanide). The synthesis of the related nitriles (*S*)- and (*R*)-**41** has already been shown in Scheme 5, whereas (*R*)-**62** was obtained from (*R*)-**43** by protection of the alcohol as the *p*-methoxybenzyl ether (PMB).

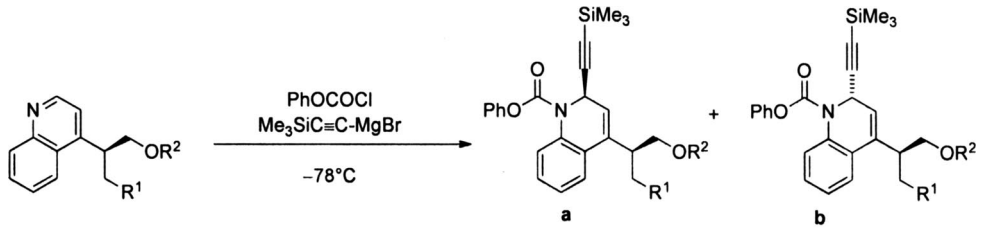
In principle, the cyano groups in the nitriles **57**, **41** and **62** could be converted into the corresponding alcohols either before or after the Yamaguchi reaction. However, preliminary experiments have shown that addition of trimethylsilyl acetylide onto the nitriles **57** or **41** results in low yields. Direct reduction of the nitriles **57**, **41** and **62** to the primary alcohols is not possible. We therefore employed a two-step procedure, first reducing the nitriles to aldehydes with DIBALH and then completing the reduction with $NaBH_4$. Isolation of the intermediate aldehydes was essential, because $NaBH_4$ treatment of the crude products gave only poor yields, probably because the intermediate aluminium imines were hydrolysed only slowly in methanol. Finally, introduction of the second protecting groups gave compounds **59**, **61** and **64**. In the case of **61** both enantiomers were prepared, thanks to the fact that both starting materials – (*S*)- or (*R*)-**41** – had been synthesised as described in Scheme 5. The stereodivergency of the starting monoacetate **18** should in principle also allow both enantiomers of **59** and **64** to be generated, although this concept has not been yet implemented.

The results of diastereoselective Yamaguchi additions to **59**, **61** and **64** are reported in Table 1. For comparison, and in order to give a comprehensive picture, we also report the results of addition to the allyl derivative **45**, as well as other representative data previously collected and published by us.[40] It is worth noting that the diastereoselection in these



Scheme 8. *Reagents and conditions*: a) TsCl, Et_3N, CH_2Cl_2, room temp.; b) KCN, nBu_4NI, DMSO, 100 °C; c) DIBALH, toluene/CH_2Cl_2, –70 °C; d) $NaBH_4$, MeOH, –40 °C→–10 °C; e) TES-OTf, 2,6-lutidine, CH_2Cl_2, 0 °C; f) Ac_2O, pyridine/CH_2Cl_2, room temp.; g) NaH, *p*(MeO)$C_6H_4CH_2Cl$, DMF, 0 °C; h) TBDMS-Cl, imidazole, DMF, room temp.

Table 1. Protecting-group-controlled diastereoselective Yamaguchi reactions with various quinolines.[a]



Entry	Starting quinoline	Addition products	R^1	R^2	*dr*	% Yield
1	**59**	**65a**, **65b**	CH_2OTES	Tr	82:18	79
2	**61**	**66a**, **66b**	CH_2OAc	TBDMS	82:18	95
3	**64**	**67a**, **67b**	$CH_2OTBDMS$	PMB	74:26	93
4	**45**	**46a**, **46b**	$CH{=}CH_2$	TBDMS	61:39	77
5	**19**	**22a**, **22b**	OAc	Tr	70:30	94
6	**20**	**23a**, **23b**	OTES	Tr	60:40	87
7	**21**	**24a**, **24b**	OAc	MMTr	70:30	44
8	see ref.[40]	see ref.[40]	H	Tr	84:16	98
9	see ref.[40]	see ref.[40]	H	TBDMS	68:32	87

[a] For the sake of clarity all additions are listed as if carried out on the enantiomer of starting quinoline indicated in the figure, although some were actually carried out either on its enantiomer or on the racemic mixture.

additions represents long-range 1,4 asymmetric induction. In addition, the starting stereogenic centre is located outside the ring, in a conformationally mobile appendage. Finally, the two substituents R^1CH_2 and R^2OCH_2 are differentiated only two or three atoms away from the stereogenic centre. The obtainment of diastereomeric ratios of around 5:1, as with compounds **59** and **61**, must thus be considered an exceptionally good result. A similar *dr* had previously been obtained only with the unsubstituted compounds (R^1 = H), and only when the oxygenated arm was protected as the bulky trityl ether (see Entries 8 and 9). In a previous paper[40] we have proposed a model to explain the observed outcome (Figure 1). According to this model, the benzylic hydrogen is directed toward the *peri* hydrogen, slightly tilted away (30°) from the aromatic plane. Of the other two substituents, the larger (L) is orthogonal to the aromatic ring, whereas the smaller (M) is on the other side of the plane, but with a narrower angle (about 30° as the benzylic hydrogen). Obviously the nucleophile prefers to attack from the face opposite to the "large" group.

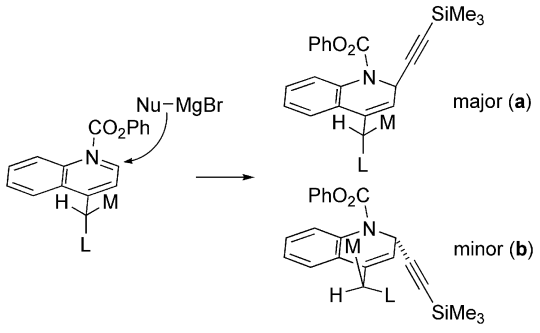
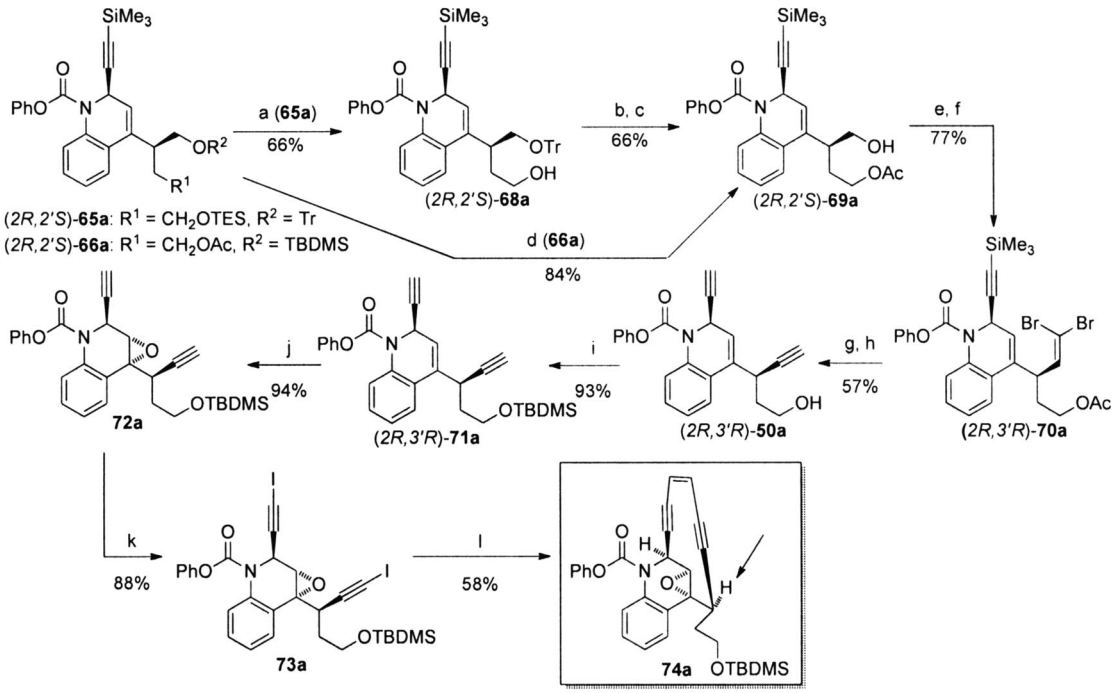


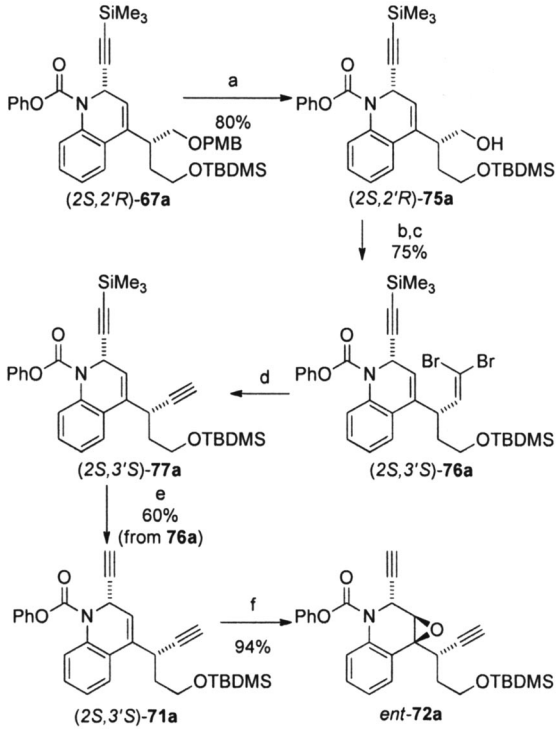
Figure 1. Model for explaining the diastereoselectivity.

This purely steric model cannot fully explain our present results, however. If we compare Entry 2 with Entry 9 or Entry 2 with Entry 4, it is hard to explain the higher selectivity observed in Entries 2–9 by assuming that a methyl or an allyl group is larger than a CH_2OAc group. The acetoxy group therefore probably plays an active role, perhaps through coordination of magnesium, favouring approach of the nucleophile from the same side of the ring. This assistance seems to be operating only when the acetoxy group is on the longer arm, as suggested by the lower *dr* obtained in the case of compound **19**, notwithstanding the greater bulkiness of a trityl group in relation to a TBDMS group.

With regard to the assessment of relative configuration, compounds **65a**, **65b**, **66a**, **66b**, **67a** and **67b** were first of all internally correlated through the transformations depicted below in Schemes 9 and 10. The products **46a** and **46b** were similarly chemically correlated to **66a** and **66b** through transformation into the common intermediate **50a** (Scheme 6). Finally, the relative configurations of compounds **22**–**24a** and **24b** had already been demonstrated.[40] We therefore had only to correlate **46** or **65**–**67** with **22**–**24**, which was achieved by finding a series of clear similarities in their ^1H NMR spectra. In particular we compared **22**–**24** with compounds **46**, **66** and **67** (in the case of **65a** and **65b** the two diastereoisomers could not be separated at this level). These characteristic NMR features may again be explained by considering a preferred conformation with the benzylic hydrogen directed towards the *peri* hydrogen, with the C–H bond forming an angle of about 30° with the ring plane (see Figure 1). In the addition products, it is reasonable to assume that the orthogonal position (with respect to the aromatic ring) is occupied by the group opposite to the alkyne (the "large" group in isomer **a** and the "medium" one in isomer **b**). This group should experience a



Scheme 9. *Reagents and conditions*: a) HF, CH_3CN/H_2O, –18 °C; b) *p*TSA, MeOH, room temp.; c) *Candida antarctica* lipase, vinyl acetate, room temp.; d) HF, CH_3CN/H_2O, 0 °C; e) $(COCl)_2$, DMSO, $EtN(iPr)_2$, CH_2Cl_2, –78 °C; f) CBr_4, PPh_3, CH_2Cl_2, –78 °C→–40 °C; g) *n*BuLi, THF, –78 °C; h) K_2CO_3, MeOH, 0 °C; i) TBDMS-Cl, imidazole, DMF, room temp.; j) *m*CPBA, CH_2Cl_2, room temp.; k) I_2·morpholine, benzene; l) (*Z*)-Me_3Sn–CH=CH–$SnMe_3$, LiCl, $Pd(PPh_3)_4$, DMF (0.01 M), 70 °C.



Scheme 10. *Reagents and conditions*: a) DDQ, CH_2Cl_2/H_2O, room temp.; b) $(COCl)_2$, DMSO, $EtN(iPr)_2$, CH_2Cl_2, –78 °C; c) CBr_4, PPh_3, CH_2Cl_2, –78 °C→–40 °C; d) *n*BuLi, THF, –78 °C; e) $AgNO_3$, $EtOH/H_2O$, KCN, 0 °C; f) *m*CPBA, CH_2Cl_2, room temp.

shielding anisotropic effect by the aromatic ring and its protons should resonate upfield. This feature is common to all the Yamaguchi adducts prepared previously with relative configurations that were established by chemical correlation, and is also perfectly reproduced in the new compounds reported here. In the major isomers **46a**, **66a** and **67a** the group opposite to the alkyne is the CH_2OR moiety, and the CH_2OR protons therefore resonate, as multiplets, at δ = 3.51–3.66, 3.51–3.68 and 3.35–3.55 ppm, whereas in the minor isomers **b** the same protons fall at δ = 3.72–3.87, 3.78–3.88 and 3.58–3.75 ppm. On the other hand, in the minor isomers **46b**, **66b** and **67b** the group opposite to the alkyne is the CH_2CH_2OR arm. The CH_2 nearest to the branching point in each case falls at δ = 2.20–2.47, 1.88–2.10 and 1.65–1.98 ppm, whereas in the major isomers **a** the same protons resonate at δ = 2.38–2.62, 1.95–2.21 and 1.85–2.08 ppm. The relative configuration was further corroborated by the NMR spectrum of the final compound **74a**, in which the chemical shift of the proton indicated by an arrow (Scheme 9) is highly diagnostic.[21]

In the cases of the adducts **66a**, **66b**, **67a** and **67b** the pairs of diastereomers could be separated by chromatography. For **65a** and **65b**, in contrast, separation was possible only after removal of the TES group to give **68a** and **68b**. In every case the synthesis was continued only on the major diastereoisomer **a**.

For our purposes, the protecting group residing on the shorter arm should be removed first. In the case of **65a**, however, this was not possible, analogously with what had

happened with **23a** (see above). We therefore removed both groups, confident of being able to acetylate the hydroxy group on the longer arm selectively by enzymatic means. *Candida antarctica* lipase showed a moderate selectivity, whereas other enzymes (e.g., Amano PS lipase) were found to be inert towards the diol. Although the moderate yield could probably be optimised, we found out that the same acetate **69a** could be obtained more efficiently in just one step from the adduct **66a** by desilylation. The synthesis of **69a** through the quinoline **61** and the Yamaguchi adduct **66a** is more convenient both in terms of step economy and of the higher overall yields obtained (see also Table 1, Entry 1). On the other hand, the stereoselectivity is identical.

Compound **69a** was converted in good overall yields into the alcohol (2*R*,3′*R*)-**50a**, taking advantage of the previous experience gained in the crucial Corey–Fuchs reaction and the subsequent *n*BuLi-promoted elimination. During this latter reaction, we also observed the formation of variable amounts of the corresponding alcohol originating from attack of *n*BuLi at the acetyl group. We therefore preferred to treat the crude product directly with K_2CO_3 in methanol to bring about complete ester solvolysis and simultaneous removal of the Me_3Si group. It is worth noting that these quite mild conditions for alkyne desilylation are not general for trimethylsilylalkynes,[68] being a particular feature of these systems.[21] The enantiomeric excess of alcohol (2*R*,2′*R*)-**50a** was determined by NMR analysis of its Mosher's ester, which indicated an *ee* of about 94%, similar to that of the starting monoacetate **18**. After reinstallation of the TBDMS group, a perfectly suited protecting group for the handle, the synthesis was completed in three efficient steps: epoxidation, introduction of the two alkynylic iodides by use of iodine-morpholine complex,[69] and finally Danishefsky–Stille double cross-coupling[36] with (*Z*)-*bis*-(trimethylstannyl)ethylene.[70] For this last reaction we took advantage of the previously optimised reaction conditions,[21] involving in particular the addition of anhydrous LiCl.[71]

^{1}H NMR analysis of the enediyne **74a** allowed confirmation of its relative configuration. In particular, it is well known that in this diastereoisomeric series the C*H* indicated by an arrow (Scheme 9) resonates at 3.0–3.1 ppm, because it falls in the shielding cone of the aromatic ring, whereas in the epimers it resonates at about 3.9–4.0 ppm.[21] In **74a** the chemical shift is indeed 3.08 ppm. Moreover, the sign of optical rotation of 7**4a** (+394.2) is the same as that of natural dynemicin and also of the simplified dynemicin analogues with the same absolute configuration.[23,24,72]

The preparation of **74a** represents the first asymmetric synthesis of a simplified dynemicin analogue. It is worth noting that, to the best of our knowledge, enantiomerically pure simplified analogues **1** had been prepared in only two cases.[23,24] These methodologies did not involve true asymmetric synthesis, but the classical resolution of synthetic intermediates. The synthesis reported here involves 17 steps from monoacetate **18** with a remarkably good overall yield of 7.2%. Moreover, the synthetic route can be easily adapted to the synthesis of the enantiomer, from the same starting monoacetate (*S*)-**18**. We have indeed already prepared the needed quinoline intermediate (*R*)-**61** from (*R*)-**41** (Scheme 8). The syntheses of (*S*)-**61** and of (*R*)-**61** are comparable: 49% and 37% overall yields, respectively (seven steps in both cases).

For the preparation of the enantiomer of **74a** we also considered use of the PMB-protected quinoline (*R*)-**64**. Its preparation from (*S*)-**18** again involves seven steps and a 38% overall yield. However, its transformation into the final product *ent*-**74a** was expected to be more step-economical (only nine steps instead of 10) and atom-economical, thanks to the fact that the final TBDMS protection is installed at the correct place from the beginning. Moreover, the slightly lower diastereoselectivity could be useful in view of the obtainment of the minor diastereoisomer *ent*-**74b**.

The transformation of the major Yamaguchi adduct **67a** into the common intermediate **71a** is shown in Scheme 10. After oxidative removal of the PMB group, the usual Corey–Fuchs protocol furnished compound **77a**. Desilylation was carried out this time with $AgNO_3$, because we were concerned about the stability of the TBDMS group in the presence of K_2CO_3. Compound (2*S*,3′*S*)-**71a** was obtained in good overall yield from **67a** and in 25% overall yield (six steps) from (*R*)-**64** [for comparison, (2*R*,3′*R*)-**71a** was prepared from (*S*)-**61** in 24% yield over seven steps]. When we measured the $[\alpha]_D$ of this intermediate, however, we found a value of –108.8, whereas the previously obtained (2*R*,3′*R*)-**71a** had +244.3. In order to check this further, we also converted (2*S*,3′*S*)-**71a** into *ent*-**72a**, but again the $[\alpha]_D$ was only –59.7 (**72a** had +129.2). From these values, and from the measured *ee* of 94% for (2*R*,3′*R*)-**50a**, the optical purities of (2*S*,3′*S*)-**71a** and *ent*-**72a** would be only about 43%.

Evidently some racemisation had occurred during the synthesis. Racemisation in the steps following the Yamaguchi addition is very unlikely, because, with two stereogenic centres, epimerisation rather than racemisation would have been observed. Moreover, the stereochemical integrity was checked at the level of the alcohol (*R*)-**43**. The critical step must therefore be either the introduction of the PMB protecting group (which employs the strong base NaH) or the nitrile reduction. From the $[\alpha]_D$ values of compounds (*R*)-**62** (–40.3) and (*R*)-**63** (–20.4), we feel that the critical step is the second one. Therefore, although this alternative combination of protecting groups has been demonstrated to work from the chemical point of view, partial loss of stereochemical integrity is an important drawback.

For now the best route for both enantiomers of **74a** remains that with use of TBDMS on the shorter arm and Ac on the longer one. The good stereoselection, however, makes this route not well suited for the synthesis of the two enantiomers of **74b**. The data collected in Table 1 and the interpretation of the stereochemical outcome might afford valuable suggestions on possible combinations of protecting groups that could lower, or even invert, the diastereoselectivity. We should keep in mind, however, that the choice of protection is not unrestricted: the experience gained from all the efforts described here has shown that there are many limitations, not only because of the need for orthogonality,

but also because introduction/removal of the blocking groups must take account of the high susceptibilities of compounds of the quinoline series to racemisation and of those of the dihydroquinoline series to epimerisation or re-aromatisation processes.

Conclusions

Despite the many problems that arose during this synthetic study, we have succeeded in developing, in good overall yield, the first enantioselective synthesis of a simplified dynemicin analogue not based on resolution methodologies.[23,24] Moreover, the product obtained has a functionalised side-arm potentially exploitable either for attachment of DNA-complexing moieties or for exploration of innovative triggering devices.

Experimental Section

NMR spectra were measured at room temp. in $CDCl_3$ at 200 MHz (^1H) or 50 MHz (^{13}C), with TMS as internal standard for ^1H NMR and the central peak of $CDCl_3$ (at δ = 77.02 ppm) for ^{13}C NMR spectroscopy. Chemical shifts are reported in ppm (δ scale); coupling constants are reported in Hertz. Peak assignments were made with the aid of DEPT experiments. In ABX systems the proton A is considered upfield and B downfield. GC-MS were carried out with an HP-1 column (11.85 m long, 0.2 mm wide), electron impact at 70 eV, and a mass temperature of about 170 °C. Only $m/z > 33$ were detected. All analyses were performed (unless otherwise stated) with a constant He flow of 0.9 mL min^{-1} with an initial temp. of 100 °C, init. time 2 min, rate 20 °C min^{-1}, final temp. 280 °C, inj. temp. 250 °C, det. temp. 280 °C. TLC analyses were carried out on silica gel plates and viewed under UV (254 nm) or developed by dipping into a solution of $(NH_4)_4MoO_4{\cdot}4H_2O$ (21 g) and $Ce(SO_4)_2{\cdot}4H_2O$ (1 g) in H_2SO_4 (31 mL) and H_2O (469 mL) and warming. R_f values were measured after elution of 7–9 cm. Column chromatography was carried out with the "flash" methodology and 220–400 mesh silica. IR spectra were recorded as $CHCl_3$ solutions. Melting points are uncorrected. Petroleum ether (40–60 °C) is abbreviated as PE. In extractive workup, aqueous solutions were always reextracted thrice with the appropriate organic solvent. Organic extracts were always dried with Na_2SO_4 and filtered, before evaporation of the solvent under reduced pressure. All reactions employing dry solvents were carried out under nitrogen (or argon where indicated). Lipase from recombinant *Candida antarctica* was a kind gift from Novo Nordisk. Amano PS lipase was a kind gift of Amano–Mitsubishi Italia.

Phenyl (2*R*)-4-[(*S*)-1-Acetoxy-3-hydroxyprop-2-yl]-2-[(trimethylsilyl)-ethynyl]-1,2-dihydroquinoline-1-carboxylate (25a)

With pTSA in MeOH: A solution of **22a**[40] (51 mg, 72.2 μmol) in dry MeOH (2 mL) was cooled to 0 °C and treated with *p*TSA (14 mg, 73.6 μmol). After 5 min the reaction mixture was allowed to stir at room temp. for 5 h. After addition of solid $NaHCO_3$ (6.2 mg, 73.6 μmol), MeOH was removed under reduced pressure without heating. The crude product was partitioned between water and AcOEt, extracted with AcOEt and washed with brine. After solvent removal, the mixture was chromatographed (PE/Et_2O 3:7 to Et_2O) to give **25a** (9.4 mg, 28%) and **26** (18.5 mg, 61%) as white foams.

With $ZnBr_2$: Dry $ZnBr_2$ (2.252 g, 10 mmol) was dissolved in dry CH_2Cl_2/*i*PrOH (85:15, 10 mL). After the mixture had been cooled to 0 °C, **22a** (141 mg, 200 μmol) was added and the resulting yellow solution was stirred at room temp. for 2 h. After quenching with aqueous KH_2PO_4 (0.5 M), the reaction was extracted with Et_2O, followed by concentration and chromatography as above to give **25a** (74 mg, 80%).

Compound 25a: R_f = 0.34 (PE/Et_2O 3:7). ^1H NMR (200 MHz, $CDCl_3$): δ = 0.04 [s, 9 H, $(CH_3)_3Si$], 2.12 (s, 3 H, $COCH_3$), 3.33 (quint., J = 5.7 Hz, 1 H, 2′-H), 3.69 and 3.72 (AB part of an ABX syst., J_{AB} = 11.2, J_{AX} = 6.0, J_{BX} = 4.4 Hz, 2 H, CH_2OH), 4.42 and 4.54 (AB part of an ABX syst., J_{AB} = 11.4, J_{AX} = 7.3, J_{BX} = 5.5 Hz, 2 H, CH_2OAc), 5.94 and 6.03 (AB syst., J = 6.9 Hz, 1 H, 2-H and 3-H), 7.18–7.46 (m, 8 H), 7.77 (br. d, J = 7.0 Hz, 2 H, 5-H or 8-H) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = –0.3 (CH_3Si), 21.0 (CH_3CO), 40.8 (C-2′), 44.9 (*C*HN), 61.9, 63.6 (CH_2OH and CH_2OAc), 89.0, 100.8 ($C{\equiv}C$), 121.6 (×2), 122.9, 125.1, 125.8, 128.1, 129.4 (×3, aromatic *C*H and C-3), 127.0, 132.7, 134.4, 150.9 (quat.), 151.9, 171.4 (*C*=O) ppm. IR: $\tilde{\nu}_{max}$ = 3504, 3004, 2957, 2274, 1722, 1599, 1481, 1328, 1289, 1222, 1186, 1163, 1011, 842 cm^{-1}. GC-MS (standard conditions but with final temp. 290 °C): R_t = 12.22 min. MS: m/z (%) = 463 (6.3) $[M]^+$, 386 (15), 347 (10), 346 (34), 252 (8.7), 236 (5.0), 226 (5.7), 192 (5.2), 180 (14), 151 (5.4), 117 (14), 94 (5.2), 77 (42), 75 (40), 73 (100), 65 (5.6), 59 (8.1), 51 (5.5), 45 (10), 43 (72). $C_{26}H_{29}NO_5Si$ (463.60): calcd. C 67.36, H 6.31, N 3.02; found C 67.45, H 6.35, N 3.08.

Compound 26: R_f = 0.11 (PE/Et_2O 3:7). ^1H NMR (200 MHz, $CDCl_3$): δ = 0.04 [s, 9 H, $(CH_3)_3Si$], 2.46 (br. s, 2 H, O*H*), 3.25 (centre of m, 1 H, 2′-H), 3.84 and 3.91 (AB part of an ABX syst., J_{AB} = 10.8, J_{AX} = 7.6, J_{BX} = 4.4 Hz, 2 H, CH_2OH), 4.15–3.98 (m, 2 H, CH_2OH), 5.92 and 5.94 (AB syst., J = 6.7 Hz, 2 H, 2-H and 3-H), 7.17–7.48 (m, 8 H), 7.75 (br. d, J = 7.0 Hz, 1 H, 5-H or 8-H) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 0.3 (CH_3Si), 42.7 (C-2′), 44.8 (*C*HN), 64.8, 64.9 (2 C, CH_2OH), 89.1, 101.5 ($C{\equiv}C$), 120.4, 121.6 (×2), 123.0, 125.1, 125.9, 128.1, 129.4 (×2), 129.6 (aromatic *C*H and C-3), 127.1, 133.1, 134.3, 150.8 (quat.), 151.9 (*C*=O) ppm. IR: $\tilde{\nu}_{max}$ = 3605, 3431, 3001, 2955, 2169, 1710, 1598, 1481, 1452, 1381, 1162, 1135, 1005, 962, 841 cm^{-1}. GC-MS (usual method but with final temp. 290 °C): R_t = 12.00 min. MS: m/z (%) = 421 (5.9) $[M]^+$, 347 (11), 346 (32), 345 (5.4), 344 (14), 328 (6.0), 280 (11), 264 (5.7), 252 (11), 236 (5.9), 226 (6.6), 206 (5.7), 180 (13), 172 (5.1), 165 (5.2), 156 (5.7), 155 (5.4), 151 (6.3), 115 (5.3), 97 (5.3), 94 (14), 83 (5.2), 77 (41), 75 (28), 73 (100), 65 (6.9), 59 (6.3), 51 (6.6), 45 (14), 43 (13), 39 (5.8). $C_{24}H_{27}NO_4Si$ (421.56): calcd. C 68.38, H 6.46, N 3.32; found C 68.29, H 6.50, N 3.40.

Phenyl (2*R*)-4-[(*R*)-1-Hydroxy-3-(triphenylmethoxy)prop-2-yl]-2-[(trimethylsilyl)ethynyl]-1,2-dihydroquinoline-1-carboxylate (27a)

From Acetate 22a: The acetate **22a** (85 mg, 120 μmol) was dispersed in phosphate buffer (pH 7)/heptane (20 mL, 85:15). After addition of lipase from *Candida antarctica* (87 mg) the mixture was vigorously stirred at 60 °C for 31 h. The enzyme was filtered through a celite pad and the crude product was extracted with Et_2O and washed with brine. After solvent removal and chromatography (PE/Et_2O 7:3), compound **27a** (49 mg, 61%) was obtained as a white foam together with 20 mg of unreacted starting material (24%).

From Triethylsilyl Ether 23a: This transformation has already been reported.[40]

Spectroscopic data for compound **27a** have already been reported.[40]

Phenyl (2*R*)-4-[(*S*)-1-Methoxymethoxy-3-(triphenylmethoxy)prop-2-yl]-2-[(trimethylsilyl)ethynyl]-1,2-dihydroquinoline-1-carboxylate (28a): A solution of **27a** (101 mg, 152 μmol) in dry CH_2Cl_2 (5 mL) was cooled to 0 °C and treated with *N*,*N*-diisopropylethylamine

(44 μL, 253 μmol) and chloromethyl methyl ether (17 μL, 224 μmol). The reaction mixture was then allowed to stir at room temp. and the same amount of both reagents was added twice, after 20 and 30 h respectively, in order to achieve complete consumption of the substrate. The resulting solution was partitioned between water and Et_2O and extracted. After solvent removal and chromatography (PE/Et_2O 9:1 to 8:2), **28a** (92 mg, 85%) was obtained as a white foam. R_f = 0.35 (PE/Et_2O 8:2). $[a]_D$ = +188.1 (*c* = 2.1, $CHCl_3$). ^1H NMR (200 MHz, $CDCl_3$): δ = 0.02 [s, 9 H, $(CH_3)_3Si$], 3.26–3.40 (m, 3 H, $CHCH_2OTr$), 3.28 (s, 3 H, OCH_3), 3.86–4.02 (m, 2 H, CH_2OMOM), 4.58 and 4.58 (AB syst., J = 7.2 Hz, 2 H, OCH_2OCH_3), 5.94 and 5.94 (AB syst., J = 7.2 Hz, 2 H, 2-H and 3-H), 6.91–7.35 (m, 23 H), 7.77 (br. d, J = 7.2 Hz, 1 H, 5-H or 8-H) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = –0.2 (CH_3Si), 40.2 (C-2′), 44.9 (*C*HN), 55.4 (OCH_3), 62.7, 67.7 (CH_2OTr and CH_2OMOM), 86.3 ($OCPh_3$), 88.5, 101.4 ($C{\equiv}C$), 96.9 (OCH_2OCH_3), 121.7 (×3), 122.2, 123.2, 125.0, 125.6, 126.9 (×3), 127.5, 127.7 (×6), 128.6 (×6), 129.2 (×2, aromatic *C*H and C-3), 125.2, 134.4, 134.5, 143.9 (×3), 150.9 (quat.), 151.8 (*C*=O) ppm. IR: $\tilde{\nu}_{max}$ = 3004, 2955, 2926, 2172, 1713, 1484, 1448, 1379, 1325, 1288, 1196, 1020, 960, 842 cm^{-1}. GC-MS: unsuitable for this analysis. $C_{45}H_{45}NO_5Si$ (707.93): calcd. C 76.35, H 6.41, N 1.98; found C 76.55, H 6.36, N 1.90.

Phenyl (2*R*)-4-[(*S*)-1-Hydroxy-3-(methoxymethoxy)prop-2-yl]-2-[(trimethylsilyl)ethynyl]-1,2-dihydroquinoline-1-carboxylate (29a): A solution of **28a** (221 mg, 312 μmol) in dry MeOH (2 mL) was cooled to 0 °C and treated with HCl (0.1 M in MeOH, 100 μL). The reaction mixture was then allowed to stir at room temp. and the same amount of HCl was added twice, after 2 and 4 h, in order to achieve complete consumption of the substrate. After addition of aqueous $NaHCO_3$ (5%) and evaporation of MeOH the crude product was partitioned between water and Et_2O. After solvent removal and chromatography (PE/Et_2O 24:76), **29a** (99 mg, 68%) was obtained as a yellow foam. R_f = 0.37 (PE/Et_2O 24:76). $[a]_D$ = +280.8 (*c* = 1.0, $CHCl_3$). ^1H NMR (200 MHz, $CDCl_3$): δ = 0.04 [s, 9 H, $(CH_3)_3Si$], 2.27 (br. s, 1 H, O*H*), 3.32 (quint., J = 5.8 Hz, 1 H, 2′-H), 3.42 (s, 3 H, OCH_3), 3.80–4.03 (m, 4 H, CH_2OH and CH_2O-MOM), 4.72 (s, 2 H, OCH_2OCH_3), 5.93 and 5.96 (AB syst., J = 6.7 Hz, 2 H, 2-H and 3-H), 7.17–7.48 (m, 8 H), 7.76 (br. d, J = 8.4 Hz, 1 H, 5-H) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = –0.3 (CH_3Si), 41.4 (C-2′), 44.9 (*C*HN), 55.6 (OCH_3), 63.9, 69.0 (CH_2OH and CH_2OMOM), 88.8, 100.9 ($C{\equiv}C$), 96.8 (OCH_2-OCH_3), 121.6 (×2), 122.4, 123.0, 125.0, 125.7, 127.9, 129.3 (×2, aromatic *C*H and C-3), 127.2, 133.3, 134.3, 150.9 (quat.), 151.8 (*C*=O) ppm. IR: $\tilde{\nu}_{max}$ = 3542, 3002, 2953, 2171, 1715, 1483, 1453, 1379, 1327, 1304, 1187, 1106, 1018, 961, 842 cm^{-1}. GC-MS (usual method but with final temp. 290 °C): R_t = 12.14 min. *m*/*z* = 465 (3.5) $[M]^+$, 420 (6.3), 388 (15), 374 (5.0), 347 (8.3), 346 (28), 280 (11), 254 (6.2), 252 (10), 250 (6.5), 236 (5.9), 230 (5.6), 226 (5.8), 208 (5.2), 206 (5.2), 194 (6.4), 180 (14), 151 (6.0), 127 (5.5), 89 (5.5), 77 (32), 75 (16.2), 74 (6.4), 73 (71), 59 (8.8), 45 (100). $C_{26}H_{31}NO_5Si$ (465.61): calcd. C 67.07, H 6.71, N 3.01; found C 67.25, H 6.76, N 3.11.

(*S*)-4-[(*tert*-Butyldimethylsilyl)oxy]-3-(quinolin-4-yl)butanenitrile [(*S*)-41]: A solution of the alcohol (*R*)-**40**[39] ($[a]_D$ = +35.6, *c* = 1.5 $CHCl_3$, *ee* = 97%, 3.054 g, 9.62 mmol) in dry CH_2Cl_2 (10 mL) was cooled to 0 °C and treated with pyridine (10 mL) and with *p*-toluenesulfonyl chloride (2.608 g, 13.7 mmol). After 5 min the cooling bath was removed and the mixture was stirred for 5 h at room temp. After quenching with H_2O (50 mL), the pH was adjusted to 8 by addition of solid $NaHCO_3$, and the aqueous phase was extracted twice with Et_2O and once with AcOEt. After washing with brine, evaporation (in order to remove pyridine completely, azeotropic evaporation with *n*-heptane was employed) gave the crude tosylate (4.55 g). This was taken up in dry DMSO (15 mL), treated with nBu_4NI (715 mg, 1.94 mmol) and KCN (1.864 g, 28.6 mmol) and warmed at 60 °C for 2 h and 40 min. At this point the conversion was complete (in order to separate **41** from the starting tosylate by tlc it is necessary to use a 15 cm plate with PE/Et_2O/CH_2Cl_2 4:3:3 as eluent and to carry out a double run). The solution was poured into a mixture of water and brine (1:1). Extraction with Et_2O (twice) and then with AcOEt (twice), followed by washing with brine, concentration and chromatography (PE/Et_2O 6:4 to 4:6), gave pure (*S*)-**41** as an oil (2.626 g, 84%). The preparation of this compound from the monoacetate **18** can be carried out (four steps) in an overall yield of 79% without purification of the intermediates. R_f = 0.51 (PE/AcOEt 1:1). $[a]_D$ = +33.9 (*c* = 1.3, $CHCl_3$). ^1H NMR (200 MHz, $CDCl_3$): δ = –0.02, –0.01 [2 × s, 2 × 3 H, $(CH_3)_2Si$], 0.87 [s, 9 H, $(CH_3)_3C$], 2.92 and 3.04 (AB part of an ABX syst., J_{AB} = 16.7, J_{AX} = 6.6, J_{BX} = 6.0 Hz, 2 H, CH_2CN), 3.84–4.11 (m, 3 H, CH_2OSi and 3′-H), 7.34 (d, J = 4.6 Hz, 1 H, 3-H), 7.63 (dt, J_d = 1.4, J_t = 7.7 Hz, 1 H, 6-H), 7.76 (dt, J_d = 1.3, J_t = 7.6 Hz, 1 H, 7-H), 8.02 (dd, J = 1.2, 8.2 Hz, 1 H, 5-H), 8.17 (dd, J = 0.6, 8.4 Hz, 1 H, 8-H), 8.90 (d, J = 4.6 Hz, 1 H, 2-H) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = –5.6 (CH_3Si), 18.2 [$C(CH_3)_3$], 19.5 (CH_2CN), 25.8 [$(CH_3)_3C$], 38.3 (C-3′), 64.4 (CH_2O), 118.1 (*C*N), 118.7 (C-3), 122.1, 127.2, 129.4, 130.8 (C-5, C-6, C-7, C-8), 126.5 (C-4a), 144.7 (C-4), 148.5 (C-8a), 149.9 (C-2) ppm. IR: $\tilde{\nu}_{max}$ = 2952, 2927, 2855, 2248, 1718, 1592, 1571, 1462, 1387, 1362, 1191, 1103, 1006, 933, 833 cm^{-1}. GC-MS: R_t = 9.51 min. MS: *m*/*z* (%) = 326 (5.6) $[M]^+$, 271 (5.6), 269 (100), 242 (14), 239 (6.9), 228 (7.9), 154 (15), 98 (12), 75 (8.0), 73 (6.8). $C_{19}H_{26}N_2OSi$ (326.51): calcd. C 69.89, H 8.03, N 8.58; found C 70.0, H 8.3, N 8.4.

(*R*)-4-[(*tert*-Butyldimethylsilyl)oxy]-3-(quinolin-4-yl)butanenitrile [(*R*)-41]: A solution of (*R*)-**43** (130.4 mg, 0.61 mmol) in dry DMF (2 mL) was cooled to 0 °C and treated with imidazole (67.9 mg, 0.99 mmol) and with *tert*-butyldimethylsilyl chloride (129.2 mg, 0.86 mmol). After 5 min the cooling bath was removed and the mixture was stirred overnight at room temp. Addition of saturated aqueous NH_4Cl (20 mL) and saturated $NaHCO_3$ (20 mL), followed by extraction with Et_2O, concentration and chromatography (PE/AcOEt 7:3), gave pure (*R*)-**43** as an oil (166.4 mg, 83%). $[a]_D$ = –32.8 (*c* = 1.5, $CHCl_3$). The other analytical data were identical to those reported above for its enantiomer.

(*R*)-4-Acetoxy-3-(quinolin-4-yl)butanenitrile [(*R*)-42]: A solution of the monoacetate **18**[39] (10.86 g, 44.3 mmol, 97% *ee*) in dry CH_2Cl_2 (24 mL) was treated with pyridine (60 mL), cooled to 0 °C and treated with *p*-toluenesulfonyl chloride (10.27 g, 53.9 mmol). After 10 min the cooling bath was removed and the solution was stirred for 5 h at room temp. After quenching with H_2O (200 mL), the pH was adjusted to 8 by addition of solid $NaHCO_3$, and the aqueous phase was extracted once with Et_2O and twice with AcOEt. After washing with brine, evaporation (in order to remove pyridine completely, azeotropic evaporation with *n*-heptane was employed) gave the crude tosylate (13.50 g). This was taken up in dry DMSO (60 mL), treated with nBu_4NI (3.173, 8.60 mmol) and KCN (5.593 g, 85.9 mmol) and stirred at room temp. for 27 h. The solution was poured into water (100 mL) and brine (100 mL). Extraction with Et_2O (once) and then with AcOEt (twice), followed by washing with brine, concentration and chromatography (PE/AcOEt 2:8), gave pure (*R*)-**42** as an oil (10.43 g, 93%). R_f = 0.47 (PE/AcOEt 20:80). $[a]_D$ = –13.8 (*c* = 2.1, $CHCl_3$). ^1H NMR (200 MHz, $CDCl_3$): δ = 2.10 (s, 3 H, CH_3CO), 2.96 (d, J = 6.2 Hz, 2 H, CH_2CN), 4.20–4.43 (m, 1 H, C*H*HOAc and 3′-H), 4.59 (dd, J = 4.4, 10.6 Hz, 1 H, C*H*HOAc), 7.33 (d, J = 4.8 Hz, 1 H, 3-H), 7.67 (dt, J_d = 1.6, J_t = 7.7 Hz, 1 H, 6-H), 7.79 (dt, J_d = 1.2, J_t = 7.7 Hz,

1 H, 7-H), 8.08 (d, J = 8.8 Hz, 1 H, 5-H), 8.19 (dd, J = 1.2, 8.0 Hz, 1 H, 8-H), 8.94 (d, J = 4.8 Hz, 1 H, 2-H) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 20.0 (CH_2CN), 20.3 (CH_3CO), 35.0 (C-3′), 65.1 (CH_2O), 117.2 (*C*N), 118.1 (C-3), 121.9, 127.3, 129.5, 130.5 (C-5, C-6, C-7, C-8), 126.1 (C-4a), 143.2 (C-4), 148.3 (C-8a), 149.8 (C-2) ppm. IR: $\tilde{\nu}_{max}$ = 3000, 2963, 1741, 1592, 1571, 1420, 1384, 1366, 1190, 1035, 907, 838 cm^{-1}. GC-MS: R_t = 8.68 min. MS: *m*/*z* (%) = 254 (20.0) $[M]^+$, 194 (14.7), 182 (34.1), 181 (40.0), 179 (6.5), 172 (6.1), 155 (14.9), 154 (100), 153 (20.7), 129 (14.8), 127 (8.4), 101 (5.0), 43 (33.1). $C_{15}H_{14}N_2O_2$ (254.28): calcd. C 70.85, H 5.55, N 11.02; found C 70.7, H 5.7, N 10.85.

(*S*)-4-Hydroxy-3-(quinolin-4-yl)butanenitrile [(*S*)-43]: A solution of (*S*)-**41** (93.5 mg, 286 μmol) in acetonitrile (2 mL) was cooled to 0 °C, and treated with aqueous HF (40%, 100 μL). The solution was stirred at 0 °C for 5 h and was then treated with saturated aqueous $NaHCO_3$ (20 mL) and extracted with Et_2O. After washing with brine, concentration and chromatography (AcOEt to AcOEt/MeOH 96:4) gave pure (*S*)-**43** as a white solid (58.2 mg, 95%); m.p. 113.8–114.8 °C. $[\alpha]_D$ = +28.2 (c = 1, acetone). The enantiomeric excess was determined by conversion into the Mosher's esters and was found to be 96%. R_f = 0.43 (AcOEt). ^{1}H NMR (200 MHz, $CDCl_3$): δ = 2.86–3.15 (m, 2 H, CH_2CN), 3.40 (br. s, 1 H, O*H*), 4.00–4.20 (m, 3 H, CH_2OH and 3′-H), 7.29 (d, J = 4.7 Hz, 1 H, 3-H), 7.57 (dt, J_d = 1.2, J_t = 6.8 Hz, 1 H, 6-H), 7.67 (dt, J_d = 1.2, J_t = 7.0 Hz, 1 H, 7-H), 7.98 (d, J = 8.4 Hz, 2 H, 5-H and 8-H), 8.74 (d, J = 4.7 Hz, 1 H, 2-H) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 19.4 (CH_2CN), 38.2 (C-3′), 63.8 (CH_2O), 118.1 (*C*N), 118.6 (C-3), 122.1, 127.3, 129.6, 130.3 (C-5, C-6, C-7, C-8), 126.4 (C-4a), 144.8 (C-4), 148.1 (C-8a), 149.8 (C-2) ppm. IR: $\tilde{\nu}_{max}$ = 3608, 3401 (br), 3003, 1709, 1592, 1571, 1499, 1417, 1357, 1175, 1063 cm^{-1}. GC-MS: R_t = 8.52 min. MS: *m*/*z* (%) = 212 (55.4) $[M]^+$, 182 (32.6), 181 (52.3), 179 (9.7), 155 (100.0), 154 (92.7), 153 (5.7), 143 (7.5), 142 (6.7), 129 (15.5), 128 (10.1), 127 (16.4), 126 (5.6), 115 (9.7), 102 (5.0), 101 (11.8), 77 (12.0), 76 (5.4), 75 (12.0), 63 (8.7), 51 (9.7), 50 (5.7), 39 (5.4). $C_{13}H_{12}N_2O$ (212.25): calcd. C 73.56, H 5.70, N 13.20; found C 73.35, H 5.8, N 13.0.

(*R*)-4-Hydroxy-3-(quinolin-4-yl)butanenitrile [(*R*)-43]: A solution of (*R*)-**42** (210.3 mg, 0.83 mmol) in THF (5 mL) and MeOH (5 mL) was cooled to 0 °C, and treated with a solution of MeONa in MeOH (1 M, 1.07 mL, 1.07 mmol). After the mixture had been stirred for 1 h at 0 °C, a solution of AcOH in MeOH (1 M, 1.25 mL) and Et_3N (115 μL) were added. Concentration to dryness, followed by chromatography (AcOEt to AcOEt/MeOH 96:4), gave pure (*R*)-**43** as a white solid (133 mg, 76%); m.p. 114.4–115.2 °C. $[\alpha]_D$ = –28.9 (c = 1.7, acetone). The other analytical data were identical to those reported above for the enantiomer. The enantiomeric excess was determined by conversion into the Mosher's esters and was found to be 96%.

(*S*)-4-[(*tert*-Butyldimethylsilyl)oxy]-3-(quinolin-4-yl)butenal [(*S*)-44]: A solution of (*S*)-**41** (855 mg, 2.62 mmol) in dry CH_2Cl_2 (15 mL) was cooled to –78 °C and treated with a solution of diisobutylaluminium hydride in toluene (1 M, 4.3 mL). After 2 h the reaction was quenched with saturated aqueous sodium potassium tartrate (30 mL). After stirring for 1 h at room temp., extraction with AcOEt gave, after concentration and chromatography (PE/Et_2O 1:9), pure aldehyde (*S*)-**44** as an oil (723 mg, 84%). R_f = 0.21 (PE/Et_2O 2:8). $[\alpha]_D$ = +33.7 (c = 1.7, $CHCl_3$). ^{1}H NMR (200 MHz, $CDCl_3$): δ = 0.04 and 0.06 (2 × s, 2 × 3 H, CH_3Si), 0.84 [s, 9 H, $(CH_3)_3C$], 2.91–3.15 (m, 2 H, CH_2CHO), 3.77 and 3.95 (AB part of an ABX syst., J_{AB} = 9.9, J_{AX} = 6.9, J_{BX} = 4.8 Hz, 2 H, CH_2O), 4.28–4.38 (m, 1 H, 3′-H), 7.28 (d, J = 4.6 Hz, 1 H, 3-H), 7.62 (dt, J_d = 1.4, J_t = 6.2 Hz, 1 H, 6-H), 7.71 (dt, J_d = 1.4, J_t = 7.7 Hz, 1 H, 7-H), 8.13 (d, J = 5.8 Hz, 1 H, 5-H or 8-H), 8.17 (d, J = 5.4 Hz, 1 H, 5-H or 8-H), 8.85 (d, J = 4.6 Hz, 1 H, 2-H), 9.83 (t, J = 1.4 Hz, 1 H, C*H*O) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = –5.6 (CH_3Si), 18.1 [$C(CH_3)_3$], 25.7 [$(CH_3)_3C$], 35.5 (CH_2CH=), 41.4 (H-3′), 66.0 (CH_2O), 116.9 (C=CH_2), 119.2 (C-3), 123.2, 126.3, 128.8, 130.3 (C-5, C-6, C-7, C-8), 126.3 (C-4a), 135.8 (*C*H=CH_2), 148.4 (C-4), 148.9 (C-8a), 149.8 (C-2) ppm. IR: $\tilde{\nu}_{max}$ = 3021, 2949, 2927, 2855, 2729, 2474, 1724, 1589, 1570, 1462, 1386, 1360, 1200, 1101, 1005, 935, 831 cm^{-1}. GC-MS: R_t = 9.32 min. MS: *m*/*z* (%) = 329 (0.06) $[M]^+$, 272 (8.4), 198 (7.4), 181 (15), 180 (100), 168 (8.2), 154 (9.3), 101 (9.8), 75 (13), 73 (8.9), 59 (9.2). $C_{19}H_{27}NO_2Si$ (329.51): calcd. C 69.26, H 8.26, N 4.25; found C 69.4, H 8.4, N 4.15.

(*S*)-1-[(*tert*-Butyldimethylsilyl)oxy]-2-(quinolin-4-yl)pent-4-ene [(*S*)-45]: "Instant ylide" (methyltriphenylphosphonium bromide + sodium amide, Fluka cat. 69500, 468.9 mg, 1.10 mmol) was suspended in dry THF (10 mL) under Ar, stirred for 15 min at room temp. and cooled to –78 °C. A solution of aldehyde (*S*)-**44** (208.7 mg, 0.63 mmol) in dry THF (1 mL) was added. After 4 h at –78 °C the reaction was complete and it was quenched with AcOH in Et_2O (1 M, 2.2 mL). The mixture was stirred for 15 min at room temp., treated with Et_3N (500 μL), evaporated to dryness and chromatographed immediately (PE/Et_2O 1:1 + 2% Et_3N to PE/Et_2O 3:7 + 2% Et_3N) to give pure (*S*)-**45** as an oil (188 mg, 91%). ***Important note*:** This reaction was found to be rather erratic. Although we obtained good yields in five instances, in two other cases, although the reaction seemed clean as usual in tlc, a poor yield was obtained after chromatography. This annoying behaviour is probably due to decomposition pathways activated by the excess phosphorane and by silica. Rapid chromatography, in the presence of Et_3N, is therefore essential. R_f = 0.74 (PE/AcOEt 1:1). $[\alpha]_D$ = +31.0 (c = 1.3, $CHCl_3$). ^{1}H NMR (200 MHz, $CDCl_3$): δ = –0.11 (s, 6 H, CH_3Si), 0.80 [s, 9 H, $(CH_3)_3C$], 2.55 (dt, J_d = 14.4, J_t = 7.2 Hz, 1 H, C*H*HCH=), 2.75 (dt, J_d = 14.4, J_t = 5.8 Hz, 1 H, C*H*HCH=), 3.68–3.92 (m, 3 H, CH_2O and 3′-H), 4.90–5.12 (m, 2 H, C=CH_2), 5.72 (ddt, J_d = 10.0, 17.0, J_t = 5.0 Hz, 1 H, C*H*=CH_2), 7.31 (d, J = 4.6 Hz, 1 H, 3-H), 7.56 (dt, J_d = 1.6, J_t = 7.7 Hz, 1 H, 6′-H), 7.71 (dt, J_d = 1.4, J_t = 7.7 Hz, 1 H, 7′-H), 8.12 (d, J = 9.0 Hz, 2 H, 5′-H and 8′-H), 8.85 (d, J = 4.6 Hz, 1 H, 2′-H) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = –5.6 (CH_3Si), 18.1 [$C(CH_3)_3$], 25.7 [$(CH_3)_3C$], 35.5 (CH_2CH=), 41.4 (C-2), 66.0 (CH_2O), 116.9 (C=CH_2), 119.2 (C-3′), 123.2, 126.3, 128.8, 130.3 (C-5′, C-6′, C-7′, C-8′), 126.3 (4a′-C), 135.8 (*C*H=CH_2), 148.4 (C-4′), 148.9 (C-8a′), 149.8 (C-2′) ppm. IR: $\tilde{\nu}_{max}$ = 3044, 2952, 2926, 2856, 1639, 1589, 1570, 1462, 1361, 1193, 1103, 916, 831 cm^{-1}. GC-MS: R_t = 8.78 min. MS: *m*/*z* (%) = 327 (0.1) $[M]^+$, 312 (2.6), 270 (100.0), 254 (6.0), 252 (7.4), 240 (3.9), 228 (9.2), 196 (33.7), 168 (6.9), 154 (11.7), 75 (9.7), 73 (9.9). $C_{20}H_{29}NOSi$ (327.54): calcd. C 73.34, H 8.92, N 4.28; found C 73.4, H 8.9, N 4.25.

Phenyl (2*R*)- and (2*S*)-4-[(*S*)-1-Hydroxypent-5-en-2-yl]-2-[(trimethylsilyl)ethynyl]-1,2-dihydroquinoline-1-carboxylates (46a and 46b): A solution of trimethylsilylacetylene (355 μL, 2.56 mmol) in dry THF (4 mL) was cooled to 0 °C and treated with EtMgBr in Et_2O (3 M, 800 μL, 2.40 mmol). In another flask, the quinoline (*S*)-**45** (419.5 mg, 1.28 mmol) was dissolved in dry THF (4 mL), cooled to –78 °C and treated with the above solution of trimethylsilylethnynylmagnesium bromide (3.5 mL, about 1.75 mmol). After 1 min, phenyl chloroformate (240 μL, 1.92 mmol) was added. The mixture was stirred at –78 °C for 2.5 h and was then poured into saturated aqueous NH_4Cl and extracted with Et_2O. Concentration and chromatography gave an inseparable diastereoisomeric mixture of the addition products (R_f = 0.41 and 0.43, PE/Et_2O 9:1, 540 mg, 77%). The diastereomeric ratio, determined by ^{1}H NMR, was 60.5:39.5 (with the less polar product prevailing).

This mixture was taken up in CH_3CN (7 mL) and cooled to 0 °C, then aqueous HF (40%, 350 μL) was added. After 3 h the mixture was treated with saturated aqueous $NaHCO_3$ (17 mL) and extracted with Et_2O. After washing with brine, concentration and chromatography (PE/Et_2O 6:4 to 1:1) gave pure (2*R*,2′*S*)-**46a** (218 mg, 51%, R_f = 0.27, PE/Et_2O 1:1) and (2*S*,2′*S*)-**46b** (142 mg, 33%, R_f = 0.40, PE/Et_2O 1:1). The overall yield of **46a** and **46b** from **45** was 65%.

Compound (2*R*,2′*S*)-46a: $[a]_D$ = +408.9 (*c* = 2.3, $CHCl_3$). ^{1}H NMR (200 MHz, $CDCl_3$): δ = 0.04 (9 H, CH_3Si), 2.35–2.64 (m, 2 H, CH_2CH=), 3.10 (quint., *J* = 6.2 Hz, 1 H, 2′-H), 3.56–3.82 (m, 2 H, CH_2OH), 5.08 (dd, *J* = 1.0, 11.0 Hz, 1 H, C=CH*H*), 5.15 (dd, *J* = 1.0, 18.4 Hz, 1 H, C=CH*H*), 5.90 (ddt, J_d = 10.2, 18.4, J_t = 6.9 Hz, 1 H, C*H*=CH_2), 5.94 and 5.98 (AB syst., *J* = 7.0 Hz, 2 H, 2-H and 3-H), 7.15–7.46 (m, 8 H), 7.76 (br. d, *J* = 7.8 Hz, 1 H, 5-H or 8-H) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = –0.3 (*C*H_3Si), 34.9 (*C*H_2–CH=), 41.0 (C-2′), 45.0 (*C*HN), 64.5 (*C*H_2OH), 89.0, 101.2 (*C*≡*C*), 117.1 (C=*C*H_2), 121.6 (×2), 122.5, 123.1, 124.9 (×2), 125.8, 127.9, 129.4 (×2, aromatic *C*H and C-3), 134.6 (*C*H=CH_2), 127.6, 134.4, 135.2, 150.9 (quat.), 151.9 (*C*=O) ppm. IR: $\tilde{\nu}_{max}$ = 3597, 3040, 2957, 2169, 1712, 1637, 1593, 1482, 1450, 1379, 1327, 1300, 1242, 1162, 1138, 1004, 961, 914, 842 cm^{-1}. GC-MS: R_t = 12.45 min. MS: *m*/*z* (%) = 431 (3.4) $[M]^+$, 354 (12.1), 347 (6.2), 346 (19.1), 338 (6.2), 254 (6.1), 252 (10.8), 226 (7.9), 206 (7.4), 180 (13.6), 178 (5.4), 167 (5.3), 166 (5.4), 151 (8.5), 97 (5.5), 94 (5.8), 77 (39.6), 75 (19.6), 73 (100.0), 65 (7.5), 59 (7.4), 45 (8.7), 41 (7.3), 39 (6.7). $C_{26}H_{29}NO_3Si$ (431.60): calcd. C 72.35, H 6.77, N 3.25; found C 72.4, H 6.8, N 3.2.

Compound (2*S*,2′*S*)-46b: $[a]_D$ = –431.5 (*c* = 2.0, $CHCl_3$). ^{1}H NMR (200 MHz, $CDCl_3$): δ = 0.04 (9 H, CH_3Si), 2.37 (t, *J* = 6.7 Hz, 2 H, CH_2CH=), 3.11 (quint., *J* = 6.2 Hz, 1 H, 2′-H), 3.78–3.92 (m, 2 H, CH_2OH), 4.98–5.14 (m, 2 H, C=CH_2), 5.77 (ddt, J_d = 10.2, 17.0, J_t = 6.9 Hz, 1 H, C*H*=CH_2), 5.96 and 6.00 (AB syst., *J* = 6.8 Hz, 2 H, 2-H and 3-H), 7.15–7.48 (m, 8 H), 7.75 (br. d, *J* = 8.0 Hz, 1 H, 5-H or 8-H) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = –0.3 (*C*H_3Si), 35.5 (*C*H_2CH=), 41.2 (C-2′), 44.7 (*C*HN), 64.4 (*C*H_2OH), 88.9, 101.5 (*C*≡*C*), 116.9 (C=*C*H_2), 121.5 (×2), 121.9, 123.0, 125.0 (×2), 125.7, 127.8, 129.3 (×2, aromatic *C*H and C-3), 135.7 (*C*H=CH_2), 134.3, 135.7, 150.9 (quat., the missing signal for a quat. C atom is probably overlapped by one of the *C*H signals), 151.9 (*C*=O) ppm. GC-MS: R_t = 12.23 min. MS: *m*/*z* (%) = 431 (4.4) $[M]^+$, 354 (11.6), 347 (5.8), 346 (18.0), 338 (5.5), 254 (5.3), 252 (9.2), 226 (7.4), 206 (6.5), 180 (11.3), 167 (5.2), 151 (7.2), 94 (6.2), 83 (5.0), 77 (35.7), 75 (22.4), 73 (100.0), 65 (6.8), 59 (7.8), 51 (5.8), 45 (9.0), 43 (5.1), 41 (7.8), 39 (6.3). IR: $\tilde{\nu}_{max}$ = 3587, 3007, 2956, 2169, 1713, 1636, 1594, 1482, 1450, 1379, 1324, 1302, 1248, 1162, 1135, 1000, 962, 910, 843 cm^{-1}. $C_{26}H_{29}NO_3Si$ (431.60): calcd. C 72.35, H 6.77, N 3.25; found C 72.5, H 6.8, N 3.15.

Phenyl (2*R*)-4-[(*R*)-1,1-Dibromohexa-1,5-dien-3-yl]-2-[(trimethylsilyl)ethynyl]-1,2-dihydroquinoline-1-carboxylate (47a): A CH_2Cl_2 solution of DMSO (1.4 M, 1.58 mL, 2.21 mmol) was diluted with dry CH_2Cl_2 (5 mL), cooled under N_2 to –78 °C, and treated with a solution of $(COCl)_2$ in CH_2Cl_2 (2.08 M, 663 μL, 1.38 mmol). After 10 min, a solution of the alcohol (2*R*,2′*S*)-**46a** (239 mg, 554 μmol) in CH_2Cl_2 (5 mL) was added. After a further 10 min, *N*-ethyldiisopropylamine (867 μL, 4.98 mmol) was added and the mixture was stirred overnight at –78 °C. The mixture was rapidly poured into an Erlenmeyer flask containing aqueous $(NH_4)H_2PO_4$ (5%, 25 mL) and HCl (1 N, 5 mL, pH 3). Extraction with PE/Et_2O 1:1, washing with brine and concentration to dryness gave the crude aldehyde (252 mg), which was used as such for the subsequent Corey–Fuchs reaction.

It was taken up in dry CH_2Cl_2 (10 mL), cooled to –78 °C and treated with CBr_4 (550 mg, 1.66 mmol). A solution of PPh_3 (595 mg, 2.27 mmol) in CH_2Cl_2 (5 mL) was then slowly added dropwise over 15 min. At the end of the addition, the temperature was allowed to rise to –40 °C. After the system had been kept for 30 min at this temperature, Et_3N (1 mL) was added and the mixture was poured into aqueous $Na_2S_2O_3$ (0.4 M, 30 mL). Extraction with Et_2O, followed by washing with brine (20 mL) containing KH_2PO_4 (1 M, 3 mL) and $Na_2S_2O_3$ (0.4 M, 3 mL) and by concentration, afforded a crude product, which was chromatographed (PE/Et_2O 95:5) to give pure **47a** as a brownish oil (234 mg, 72%). R_f = 0.70 (toluene/CH_2Cl_2/Et_2O 70:29:1). ^{1}H NMR (200 MHz, $CDCl_3$): δ = 0.04 (9 H, CH_3Si), 2.38–2.70 (m, 2 H, CH_2CH=), 3.79 (q, *J* = 7.9 Hz, 1 H, 3′-H), 5.08–5.23 (m, 2 H, C=CH_2), 5.87 (ddt, J_d = 10.2, 17.2, J_t = 6.9 Hz, 1 H, C*H*=CH_2), 5.95 and 5.98 (AB syst., *J* = 6.5 Hz, 2 H, 2-H and 3-H), 6.31 (d, *J* = 9.6 Hz, 1 H, C*H*=CBr_2), 7.16–7.48 (m, 8 H), 7.75 (br. d, *J* = 7.6 Hz, 1 H, 5-H or 8-H) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = –0.2 (*C*H_3Si), 37.3 (*C*H_2CH=), 43.2 (C-3′), 44.9 (*C*HN), 89.1, 90.8, 100.9 (*C*≡*C* and *C*Br_2), 117.7 (C=*C*H_2), 121.7 (×2), 122.3, 123.3, 125.0, 125.8, 128.0, 129.4 (×2, aromatic *C*H and C-3), 134.5 (*C*H=CH_2), 127.1, 134.2, 135.4, 151.0 (quat.), 139.9 (*C*H=CBr_2), 151.9 (*C*=O) ppm. GC-MS: R_t = 12.83 min. MS: *m*/*z* (%) = 587 (2.3), 585 (3.5), 583 (2.0) $[M]^+$, 356 (2.1), 354 (3.1), 352 (1.7), 346 (5.4), 258 (4.1), 230 (6.9), 190 (4.4), 151 (7.2), 139 (18.5), 137 (14.3), 97 (4.7), 83 (4.8), 77 (35.9), 73 (100.0), 65 (8.6), 59 (6.1), 51 (5.7), 45 (6.2), 41 (7.3), 39 (5.2). $C_{27}H_{27}Br_2NO_2Si$ (585.40): calcd. C 55.40, H 4.65, N 2.39; found C 55.65, H 4.7, N 2.3.

Phenyl (2*S*)-4-[(*R*)-1,1-Dibromohexa-1,5-dien-3-yl]-2-[(trimethylsilyl)ethynyl]-1,2-dihydroquinoline-1-carboxylate (47b): This compound was prepared in 64% yield from the alcohol (2*S*,2′*S*)-**46b** by the same procedure as described above for **47a**. R_f = 0.65 (toluene/CH_2Cl_2/Et_2O 70:29:1). ^{1}H NMR (200 MHz, $CDCl_3$): δ = 0.04 (9 H, CH_3Si), 2.20–2.58 (m, 2 H, CH_2CH=), 3.77 (dt, J_d = 5.4, J_t = 8.6 Hz, 1 H, 3′-H), 4.99–5.14 (m, 2 H, C=CH_2), 5.73 (ddt, J_d = 9.6, 17.6, J_t = 6.6 Hz, 1 H, C*H*=CH_2), 5.93 (s, 2 H, 2-H and 3-H), 6.53 (d, *J* = 8.8 Hz, 1 H, C*H*=CBr_2), 7.14–7.47 (m, 8 H), 7.74 (br. d, *J* = 7.8 Hz, 1 H, 5-H or 8-H) ppm. GC-MS: R_t = 12.92 min. MS: *m*/*z* (%) = 587 (2.7), 585 (4.2), 583 (2.0) $[M]^+$, 356 (3.2), 354 (4.7), 352 (2.7), 346 (5.7), 290 (5.4), 258 (6.0), 230 (8.3), 217 (5.2), 204 (9.4), 203 (5.5), 191 (5.3), 190 (6.1), 179 (5.3), 166 (5.4), 154 (4.9), 151 (9.8), 139 (24.0), 137 (17.1), 83 (5.1), 77 (39.4), 73 (100.0), 65 (8.9), 59 (6.5), 51 (6.7), 43 (5.7), 41 (8.5), 39 (5.0). $C_{27}H_{27}Br_2NO_2Si$ (585.40): calcd. C 55.40, H 4.65, N 2.39; found C 55.7, H 4.75, N 2.3.

Phenyl (2*R*)-4-[(*R*)-Hex-5-en-1-yn-3-yl]-2-[(trimethylsilyl)ethynyl]-1,2-dihydroquinoline-1-carboxylate (48a): The dibromide (2*R*,3′*R*)-**47a** (217.4 mg, 0.37 mmol) was dissolved in dry toluene (9 mL) under Ar and cooled to –78 °C. This solution was rapidly treated with *n*BuLi in hexanes (1.6 M, 510 μL, 816 μmol). After 15 min, the reaction was quenched with AcOH in Et_2O (1 M, 1.6 mL). After 15 min the solution was poured into brine (15 mL) and saturated aqueous $NaHCO_3$ (5 mL), and extracted with Et_2O. The crude product was chromatographed (PE/Et_2O 9:1) to give pure **48a** as a yellowish oil (86.9 mg, 55%). R_f = 0.39 (PE/Et_2O 9:1). $[a]_D$ = +298.7 (*c* = 1.5, $CHCl_3$). ^{1}H NMR (200 MHz, $CDCl_3$): δ = 0.05 (9 H, CH_3Si), 2.27 (d, *J* = 2.6 Hz, 1 H, C≡C*H*), 2.46–2.74 (m, 2 H, CH_2CH=), 3.72 (ddd, *J* = 2.2, 5.2, 7.6 Hz, 1 H, 3′-H), 5.08–5.25 (m, 2 H, C=CH_2), 5.97 (ddt, J_d = 10.6, 16.4, J_t = 7.0 Hz, 1 H, C*H*=CH_2), 5.99 (d, *J* = 6.6 Hz, 1 H, 2-H), 6.22 (d, *J* = 6.6 Hz, 1 H, 3-H), 7.14–7.53 (m, 8 H), 7.76 (br. d, *J* = 7.6 Hz, 1 H, 5-H or 8-H) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = –0.2 (*C*H_3Si), 33.2 (C-3′), 38.8 (*C*H_2CH=), 45.0 (*C*HN), 71.6, 84.4, 89.0, 101.7 (*C*≡*C*–

H), 117.8 (C=*C*H$_2$), 121.7 (×2), 123.0 (×2), 124.8, 125.0, 125.8, 127.9, 129.4 (×2, aromatic *C*H and C-3), 134.6 (*C*H=CH$_2$), 134.0, 134.2, 151.0 (quat., the missing signal for a quat. C atom is probably overlapped by one of the *C*H signals), 151.9 (*C*=O) ppm. GC-MS: R_t = 11.06 min. MS: *m*/*z* (%) = 425 (6.9) [M]$^+$, 346 (75.9), 332 (5.6), 316 (5.8), 230 (7.9), 220 (6.6), 204 (6.2), 194 (21.9), 151 (7.2), 139 (7.9), 83 (6.9), 77 (25.4), 75 (7.5), 74 (9.6), 73 (100), 59 (7.2), 45 (7.1), 39 (5.8). $C_{27}H_{27}NO_2Si$ (425.59): calcd. C 76.20, H 6.39, N 3.29; found C 76.3, H 6.4, N 3.2.

Phenyl (2*S*)-4-[(*R*)-Hex-5-en-1-yn-3-yl]-2-[(trimethylsilyl)ethynyl]-1,2-dihydroquinoline-1-carboxylate (48b): This compound was obtained in 61% yield from the dibromide (2*S*,3′*R*)-**47b** by the same procedure as described above for **48a**. R_f = 0.40 (PE/Et$_2$O 9:1). $[a]_D$ = –329.5 (*c* = 1.45, CHCl$_3$). ^{1}H NMR (200 MHz, CDCl$_3$): δ = 0.04 (9 H, C*H*$_3$Si), 2.31 (dt, J_d = 14.2, J_t = 7.7 Hz, 1 H C*H*HCH=), 2.41 (d, *J* = 2.2 Hz, 1 H, C≡C*H*), 2.46–2.62 (m, 1 H, C*H*HCH=), 3.89 (centre of m, 1 H, 3′-H), 4.96–5.15 (m, 2 H, C=C*H*$_2$), 5.89 (ddt, J_d = 10.4, 17.2, J_t = 6.8 Hz, 1 H, C*H*=CH$_2$), 5.97 (d, *J* = 7.0 Hz, 1 H, 2-H), 6.42 (dd, *J* = 1.2, 6.6 Hz, 1 H, 3-H), 7.14–7.46 (m, 8 H), 7.74 (br. d, *J* not measurable, 1 H, 5-H or 8-H) ppm. ^{13}C NMR (50 MHz, CDCl$_3$): δ = –0.2 (*C*H$_3$Si), 33.3 (C-3′), 38.5 (*C*H$_2$CH=), 45.2 (*C*HN), 73.5, 83.4, 88.9, 100.8 (*C*≡*C*H), 117.3 (C=*C*H$_2$), 121.6 (×2), 122.9, 123.6, 125.0, 125.4, 125.8, 127.9, 129.4 (×2, aromatic *C*H and C-3), 134.7 (*C*H=CH$_2$), 133.7, 134.6, 151.0 (quat., the missing signal for a quat. C atom is probably overlapped by one of the *C*H signals), 151.9 (*C*=O) ppm. IR: $\tilde{\nu}_{max}$ = 3303, 3004, 2957, 1720, 1594, 1480, 1453, 1378, 1326, 1303, 1202, 1134, 1000, 971, 917, 844 cm^{-1}. GC-MS: R_t = 10.9 min. MS: *m*/*z* (%) = 425 (8.9) [M]$^+$, 220 (5.4), 194 (17.8), 154 (5.1), 139 (7.0), 83 (7.1), 77 (22.6), 75 (8.8), 74 (8.8), 73 (100), 59 (8.0), 51 (5.1), 45 (8.4), 41 (5.8), 39 (5.5). $C_{27}H_{27}NO_2Si$ (425.59): calcd. C 76.20, H 6.39, N 3.29; found C 76.5, H 6.5, N 3.2.

(*S*)-3-(Quinolin-4-yl)-4-[(triphenylmethyl)oxy]butanenitrile [(*S*)-57]

Formation of the Tosylate: A solution of the alcohol (*R*)-**56**[40] (2.70 g, 6.06 mmol) in dry pyridine (14 mL) was cooled to 0 °C and treated with *p*-toluenesulfonyl chloride (3.47 g, 18.2 mmol). It was then allowed to stir at room temp. for 4 h. The solution was partitioned between water and Et$_2$O and the pH was adjusted to 7 by addition of aqueous NaHCO$_3$ (5%). After extraction and evaporation of the solvent, residual pyridine was azeotropically removed with *n*-heptane and the crude product was purified by chromatography with PE/Et$_2$O 1:1 to 1:9 to give the expected tosylate as a white foam (3.30 g, 91%). R_f = 0.31 (PE/Et$_2$O/CH$_2$Cl$_2$ 4:3:3). $[a]_D$ = +20.8 (*c* = 1.8, CHCl$_3$). ^{1}H NMR (200 MHz, CDCl$_3$): δ = 2.38 (s, 3 H, C*H*$_3$), 3.49 (d, *J* = 6.2 Hz, 2 H, C*H*$_2$OTr), 3.98 (quint., *J* = 6.0 Hz, 1 H, 2′-H), 4.52 and 4.55 (AB part of an ABX syst., J_{AB} = 10.1, J_{AX} = 6.4, J_{BX} = 6.0 Hz, 2 H, C*H*$_2$OTs), 7.02 (d, *J* = 4.8 Hz, 1 H, 3-H), 7.12–7.72 (m, 22 H, aromatics of Tr and Ts and 5-H, 6-H, 7-H), 8.07 (dd, *J* = 8.8 Hz, 1 H and 1.0, 8-H), 8.70 (d, *J* = 4.4 Hz, 1 H, 2-H) ppm. ^{13}C NMR (50 MHz, CDCl$_3$): δ = 21.5 (*C*H$_3$), 39.5 (H-3), 63.0, 69.5 (*C*H$_2$OTr and *C*H$_2$OTs), 87.1 (O*C*Ph$_3$), 119.1 (C-3), 122.4, 126.6, 129.0, 130.4 (C-5, C-6, C-7, C-8′), 126.8 (C-4a), 127.1 (×3), 127.8 (×6), 128.4 (×6) (*C*H of Tr), 127.6 (×2), 129.6 (×2) (*C*H of Ts), 132.3 (SO$_2$*C* of Ts), 143.3 (×3, quat. Tr), 143.7 (CH$_3$*C* of Ts), 144.7 (C-4), 148.3 (C-8a), 149.6 (C-2) ppm. IR: $\tilde{\nu}_{max}$ = 2952, 2927, 2859, 1592, 1570, 1445, 1364, 1307, 1167, 1072, 975, 897 cm^{-1}. GC-MS: unsuitable for this analysis. $C_{38}H_{33}NO_4S$ (599.74): calcd. C 76.10, H 5.55, N 2.34; found C 76.25, H 5.70, N 2.38.

Formation of the Cyanide: A solution of the above tosylate (3.30 g, 5.50 mmol) in dry DMSO (15 mL) was treated with *n*Bu$_4$NI (407 mg, 1.10 mmol) and KCN (1.29 g, 28.6 mmol) and warmed at 100 °C for 2 h and 50 min. The solution was quenched with saturated aqueous NH$_4$Cl and the pH was adjusted to 8 by addition of aqueous (NH$_4$)H$_2$PO$_4$ (5%). Extraction with Et$_2$O, followed by washing with brine, concentration and chromatography (PE/Et$_2$O 6:4 to 1:9) gave pure (*S*)-**57** as a white foam (1.90 g, 76%). R_f = 0.27 (PE/Et$_2$O/CH$_2$Cl$_2$ 4:3:3). $[a]_D$ = +46.6 (*c* = 1.2, CHCl$_3$). ^{1}H NMR (200 MHz, CDCl$_3$): δ = 2.96 and 3.07 (AB part of an ABX syst., J_{AB} = 16.8, J_{AX} = 7.4, J_{BX} = 5.7 Hz, 2 H, C*H*$_2$CN), 3.54 and 3.62 (AB part of an ABX syst., J_{AB} = 9.8, J_{AX} = 7.7, J_{BX} = 4.6 Hz, 2 H, C*H*$_2$OTr), 4.03 (quint., *J* = 6.5 Hz, 1 H, 3-H), 7.18–7.37 (m, 16 H, aromatics of Tr and 3′-H), 7.54 (dt, J_d = 1.4, J_t = 7.7 Hz, 1 H, 6′-H), 7.69–7.78 (m, 2 H, 5′-H and 7′-H), 8.14 (d, *J* = 8.8 Hz, 1 H, 8′-H), 8.84 (d, *J* = 4.4 Hz, 1 H, 2-H) ppm. ^{13}C NMR (50 MHz, CDCl$_3$): δ = 19.9 (*C*H$_2$CN), 36.7 (H-3), 64.9 (*C*H$_2$O), 87.3 (O*C*Ph$_3$), 117.8 (*C*N), 118.4 (C-3), 122.1, 126.9, 129.3, 130.6 (C-5′, C-6′, C-7′, C-8′), 126.4 (4a′-C), 127.2 (×3), 127.9 (×6), 128.4 (×6) (*C*H of Tr), 143.3 (×3, quat. Tr), 144.3 (C-4′), 148.4 (C-8a′), 149.8 (C-2′) ppm. IR: $\tilde{\nu}_{max}$ = 2957, 2253, 1733, 1448, 1361, 1243, 1171, 1068, 972, 907 cm^{-1}. GC-MS (usual method but with final temp. 290 °C): R_t = 16.50 min. MS: *m*/*z* (%) = 454 (1.2) [M]$^+$, 244 (25), 243 (100), 196 (6.1), 195 (14), 183 (6.7), 166 (5.6), 165 (35), 156 (6.1), 155 (6.0), 154 (1.0), 105 (22), 77 (12). $C_{32}H_{26}N_2O$ (454.56): calcd. C 84.55, H 5.77, N 6.16; found C 84.75, H 5.80, N 6.22.

(*S*)-3-(Quinolin-4-yl)-4-[(triphenylmethyl)oxy]butan-1-ol [(*S*)-58]: A solution of (*S*)-**57** (1.45 g, 3.19 mmol) in dry CH$_2$Cl$_2$ (15 mL) was cooled to –78 °C and treated with DIBALH (1 M in toluene, 4.1 mL). After the system had been kept for 5 h at –78 °C, saturated aqueous Rochelle's salt solution was added and the mixture was stirred at room temp. until two clear, well separated layers were obtained. After extraction with Et$_2$O, followed by washing with brine and solvent evaporation, the crude aldehyde was taken up in methanol (20 mL), cooled to 0 °C and treated with NaBH$_4$ (241 mg, 6.38 mmol, added portionwise). After 2 h the reaction was quenched with aqueous saturated NH$_4$Cl and the pH was adjusted to 8 by addition of aqueous (NH$_4$)H$_2$PO$_4$ (5%). Extraction with Et$_2$O, concentration and chromatography (PE/Et$_2$O 1.9 to pure Et$_2$O) gave (*S*)-**58** as a white foam (498 mg, 34%). R_f = 0.35 (PE/Et$_2$O 4:96). $[a]_D$ = +34.4 (*c* = 1.2, CHCl$_3$). ^{1}H NMR (200 MHz, CDCl$_3$): δ = 1.94–2.38 (m, 2 H, CHC*H*$_2$), 3.43 (d, *J* = 5.8 Hz, 2 H, C*H*$_2$OTr), 3.48–3.67 (m, 2 H, C*H*$_2$OH), 3.99 (centre of m, 1 H, 3-H), 7.16–7.30 (m, 16 H, aromatics of Tr and 3′-H), 7.54 (dt, J_d = 1.0, J_t = 7.7 Hz, 1 H, 6′-H), 7.71 (dt, J_d = 1.2, J_t = 7.7 Hz, 1 H, 7′-H), 8.11 (t, *J* = 6.6 Hz, 2 H, 5'-H and 7′-H), 8.81 (br. s, 1 H, 2′-H) ppm. ^{13}C NMR (50 MHz, CDCl$_3$): δ = 35.2 (CH*C*H$_2$), 36.5 (H-3), 60.4, 67.3 (*C*H$_2$OTr and *C*H$_2$OH), 86.9 (O*C*Ph$_3$), 118.9 (C-3′), 123.3, 126.4, 129.1, 130.2 (C-5′, C-6′, C-7′, C-8′), 127.9 (4a′-C), 127.0 (×3), 127.7 (×6), 128.5 (×6) (*C*H of Tr), 143.7 (×3, quat. Tr), 148.3 (C-8a′), 149.4 (C-4′), 149.8 (C-2′) ppm. IR: $\tilde{\nu}_{max}$ = 3405, 2953, 1589, 1441, 1259, 1069, 898 cm^{-1}. GC-MS (standard conditions but with final temp. 290 °C): R_t = 16.54 min. MS: *m*/*z* (%) = 258 (1.2) [M – 201]$^+$, 244 (23), 243 (100), 200 (5.5), 165 (26), 154 (6.6), 105 (10), 77 (5.4). $C_{32}H_{29}NO_2$ (459.58): calcd. C 83.63, H 6.36, N 3.05; found C 83.80, H 6.31, N 3.15.

(*S*)-2-(Quinolin-4-yl)-4-[(triethylsilyl)oxy]-1-[(triphenylmethyl)oxy]-butane [(*S*)-59]: A solution of (*S*)-**58** (181 mg, 394 μmol) in dry CH$_2$Cl$_2$ (4 mL) was cooled to 0 °C and treated with 2,6-lutidine (101 μL, 867 μmol) and triethylsilyl triflate (125 μL, 552 μmol). After 3 h the solution was partitioned between water and Et$_2$O and the pH was adjusted to about 8 by addition of saturated aqueous NaHCO$_3$. After extraction with Et$_2$O and solvent removal, residual 2,6-lutidine was azeotropically removed with *n*-octane. Chromatography with PE/Et$_2$O 6:4 to 1:1 gave (*S*)-**59** as a yellow oil (107 mg, 47%). R_f = 0.43 (PE/Et$_2$O 1.1). $[a]_D$ = +21.4 (*c* = 1.7, CHCl$_3$). ^{1}H

NMR (200 MHz, $CDCl_3$): δ = 0.48 [q, J = 7.9 Hz, 6 H, $(CH_3CH_2)_3$-Si], 0.85 [t, J = 7.9 Hz, 9 H, $(CH_3CH_2)_3Si$], 1.99–2.28 (m, 2 H, $CHCH_2$), 3.34–3.65 (m, 5 H, $CHCH_2OTr$ and CH_2OTES), 4.02 (quint., J = 6.6 Hz, 1 H, 2-H), 7.14–7.28 (m, 16 H, aromatics of Tr and 3′-H), 7.53 (dt, J_d = 1.0, J_t = 7.4 Hz, 1 H, 6′-H), 7.71 (dt, J_d = 1.2, J_t = 7.6 Hz, 1 H, 7′-H), 8.13 (br. d, J = 8.4 Hz, 2 H, 5′-H and 7′-H), 8.82 (br. d, J = 4.8 Hz, 1 H, 2′-H) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 4.3 $[(CH_3CH_2)_3Si]$, 6.7 $[(CH_3CH_2)_3Si]$, 35.1 ($CHCH_2$), 36.1 (H-2), 60.3, 67.3 (CH_2OTr and CH_2OTES), 86.6 ($OCPh_3$), 118.9 (C-3′), 123.6, 126.1, 128.9, 130.2 (C-5′, C-6′, C-7′, C-8′, C-4a′), 126.9 (×3), 127.8 (×6), 128.6 (×6, *C*H of Tr), 143.8 (×3, quat. Tr), 148.4, 149.7, 149.8 (C-8a′, C-4′, C-2′) ppm. IR: $\tilde{\nu}_{max}$ = 2953, 2871, 1587, 1447, 1386, 1187, 1073, 898, 872 cm^{-1}. GC-MS: unsuitable for this analysis. $C_{38}H_{43}NO_2Si$ (573.84): calcd. C 79.54, H 7.55, N 2.44; found C 79.70, H 7.52, N 2.61.

(*S*)-4-[(*tert*-Butyldimethylsilyl)oxy]-3-(quinolin-4-yl)butanol [(*S*)-60]: The alcohol (*S*)-**41** (1.98 g, 6.06 mmol) was converted into the aldehyde (*S*)-**44** by the procedure already described above. The crude aldehyde was taken up in dry MeOH (15 mL), cooled to –40 °C and treated with $NaBH_4$ (1.193 g, 31.5 mmol). The temperature was allowed to rise slowly to 0 °C over 2 h. The reaction was quenched with saturated aqueous NH_4Cl. Extraction with Et_2O (twice) and AcOEt (twice), washing with brine, concentration and chromatography (PE/AcOEt 3:7) gave pure (*S*)-**60** (1.254 g, 62%). R_f = 0.15 (Et_2O). $[a]_D$ = +48.0 (c = 1.1, $CHCl_3$). ^1H NMR (200 MHz, $CDCl_3$): δ = –0.04 (s, 6 H, CH_3Si), 0.83 [s, 9 H, $(CH_3)_3C$], 1.97–2.42 (m, 2 H, CH_2CH_2OH), 3.55–3.94 (m, 5 H, CH_2O and 3-H), 7.30 (d, J = 4.6 Hz, 1 H, 3′-H), 7.57 (dt, J_d = 1.3, J_t = 7.7 Hz, 1 H, 6′-H), 7.71 (dt, J_d = 1.6, J_t = 7.7 Hz, 1 H, 7′-H), 8.08–8.21 (m, 2 H, 5′-H and 8′-H), 8.84 (d, J = 4.6 Hz, 1 H, 2′-H) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = –5.7 (CH_3Si), 18.1 $[C(CH_3)_3]$, 25.7 $[(CH_3)_3C]$, 35.3 (CH_2CH=), 38.7 (H-3), 60.5, 67.0 (CH_2O), 118.9 (C-3′), 123.1, 126.4, 129.0, 130.1 (C-5′, C-6′, C-7′, C-8′), 127.6 (C-4a′), 148.2 (C-4′), 149.5 (C-8a′), 149.7 (C-2′) ppm. IR: $\tilde{\nu}_{max}$ = 3614, 3382 (br), 2951, 2881, 2856, 1588, 1571, 1463, 1390, 1361, 1242, 1100, 906, 831 cm^{-1}. GC-MS: R_t = 9.60 min. MS: m/z (%) = 316 $[M – 15]^+$ (2.5), 300 (2.7), 274 (100.0), 244 (39.1), 241 (5.7), 200 (17.3), 182 (44.2), 180 (15.4), 170 (32.8), 168 (11.6), 167 (22.1), 156 (13.5), 154 (17.3), 105 (27.9), 89 (5.7), 75 (45.6), 73 (14.8). $C_{19}H_{29}NO_2Si$ (331.52): calcd. C 68.83, H 8.82, N 4.22; found C 70.0, H 8.9, N 4.15.

(*S*)-4-Acetoxy-1-[(*tert*-butyldimethylsilyl)oxy]-2-(quinolin-4-yl)-butane [(*S*)-61]: A solution of the alcohol (*S*)-**60** (1.101 g, 2.95 mmol) in dry CH_2Cl_2 (8 mL) was treated with pyridine (4 mL) and acetic anhydride (550 µL). After 1 h at room temp. the reaction was complete, and H_2O (10 mL) was added. After stirring for 30 min, the mixture was diluted with saturated aqueous $NaHCO_3$ and extracted with AcOEt. The organic extracts were washed with brine and the solvents were evaporated to dryness. The residue was taken up three times with CH_2Cl_2/*n*-heptane and concentrated again in order to remove pyridine completely. The crude product (1.260 g) was pure by tlc, GC-MS and ^1H NMR analyses and was therefore used as such for the preparation of **66a** and **66b**. R_f = 0.59 (Et_2O). ^1H NMR (200 MHz, $CDCl_3$): δ = –0.08 (s, 6 H, CH_3Si), 0.81 [s, 9 H, $(CH_3)_3C$], 1.93 (s, 3 H, CH_3CO), 2.04–2.45 (m, 2 H, CH_2CH_2OAc), 3.76–4.21 (m, 5 H, CH_2O and 2-H), 7.34 (d, J = 4.8 Hz, 1 H, 3′-H), 7.58 (dt, J_d = 1.6, J_t = 7.7 Hz, 1 H, 6′-H), 7.72 (dt, J_d = 1.5, J_t = 7.6 Hz, 1 H, 7′-H), 8.13 (dt, J_d = 8.2, J_t = 1.8 Hz, 2 H, 5′-H and 8′-H), 8.87 (d, J = 4.8 Hz, 1 H, 2′-H) ppm. GC-MS: R_t = 9.87 min. MS: m/z (%) = 358 (1.3) $[M – 15]^+$, 317 (9.8), 316 (39.7), 274 (32.9), 242 (5.0), 182 (25.3), 170 (6.1), 168 (8.6), 167 (13.5), 154 (12.0), 117 (100.0), 89 (9.0), 75 (50.3), 73 (29.7), 59 (8.5), 58 (5.1), 43 (28.7).

(*R*)-4-[(4-Methoxybenzyl)oxy]-3-(quinolin-4-yl)butanenitrile [(*R*)-62]: A solution of the alcohol (*R*)-**43** (3.713 g, 17.5 mmol) in dry DMF (60 mL) was cooled to 0 °C and treated portionwise with NaH in mineral oil (60%, 705 mg, 17.5 mmol). After cessation of gas evolution, *p*-methoxybenzyl chloride (2.70 mL, 19.2 mmol) was added. After 5 min the cooling bath was removed and the suspension was stirred for 30 min. After quenching with saturated NH_4Cl (80 mL), the mixture was extracted with Et_2O (twice) and AcOEt (once). The organic extracts were washed with water and then with brine. Concentration and chromatography gave pure (*R*)-**62** as an oil (5.23 g, 90%). R_f = 0.68 (AcOEt). $[a]_D$ = –40.3 (c = 1.8, $CHCl_3$). ^1H NMR (200 MHz, $CDCl_3$): δ = 2.94 and 3.01 (AB part of an ABX syst., J_{AB} = 14.9, J_{AX} = 4.5, J_{BX} = 4.2 Hz, 2 H, CH_2CN), 3.78 and 3.88 (AB part of an ABX syst., J_{AB} = 9.6, J_{AX} = 7.8, J_{BX} = 4.2 Hz, 2 H, CH_2OPMB), 3.81 (s, 3 H, OCH_3), 4.05–4.21 (m, 1 H, 3-H), 4.51 (s, 2 H, $ArCH_2$), 6.88 (d, J = 8.4 Hz, 2 H, *H ortho* to OMe), 7.24 (d, J = 8.4 Hz, 2 H, *H meta* to OMe), 7.35 (d, J = 4.6 Hz, 1 H, 3′-H), 7.61 (dt, J_d = 1.4, J_t = 7.7 Hz, 1 H, 6′-H), 7.75 (dt, J_d = 1.4, J_t = 7.5 Hz, 1 H, 7′-H), 7.97 (d, J = 8.4 Hz, 1 H, 5′-H or 8′-H), 8.17 (dd, J = 0.6, 8.4 Hz, 1 H, 5′-H or 8′-H), 8.89 (d, J = 4.6 Hz, 1 H, 2′-H) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 20.16 (CH_2CN), 36.2 (C-3), 55.2 (OCH_3), 70.6, 73.2 (CH_2O), 113.9 (*C ortho* to OMe), 117.8 (CCH_2O), 118.9 (C-3′), 122.0, 127.2, 129.4, 130.7 (C-5′, C-6′, C-7′, C-8′), 126.4 (C-4a′), 129.4 (*C meta* to OMe), 130.7 (CCH_2O), 144.5 (C-4′), 148.4 (C-8a′), 150.0 (C-2′), 159.4 (*C*OMe) ppm. IR: $\tilde{\nu}_{max}$ = 2956, 2861, 2836, 1667, 1610, 1592, 1570, 1502, 1462, 1418, 1360, 1301, 1192, 1093, 1030 cm^{-1}. GC-MS: R_t = 11.86 min. MS: m/z (%) = 332 (18.1) $[M]^+$, 331 (9.0), 156 (9.6), 154 (6.3), 136 (5.8), 121 (100.0), 78 (8.0), 77 (10.2). $C_{21}H_{20}N_2O_2$ (332.40): calcd. C 75.88, H 6.06, N 8.43; found C 75.7, H 6.1, N 8.4.

(*R*)-4-[(4-Methoxybenzyl)oxy]-3-(quinolin-4-yl)butanol [(*R*)-63]: This compound was prepared from (*R*)-**62** in 66% yield by the same procedure as described above for (*S*)-**60**. R_f = 0.33 (AcOEt). $[a]_D$ = –20.4 (c = 2.1, $CHCl_3$). ^1H NMR (200 MHz, $CDCl_3$): δ = 1.81 (br. s, 1 H, O*H*), 1.95–2.31 (m, 2 H, CH_2CH_2OH), 3.53–3.83 (4 H, CH_2OH and CH_2OPMB), 3.80 (s, 3 H, OCH_3), 3.99 (quint., J = 6.5 Hz, 1 H, 3-H), 4.46 (s, 2 H, $ArCH_2$), 6.85 (d, J = 8.8 Hz, 2 H, *H ortho* to OMe), 7.19 (d, J = 8.8 Hz, 2 H, *H meta* to OMe), 7.27 (d, J = 4.8 Hz, 1 H, 3′-H), 7.53 (dt, J_d = 1.2, J_t = 7.7 Hz, 1 H, 6′-H), 7.71 (dt, J_d = 1.4, J_t = 7.6 Hz, 1 H, 7′-H), 8.12 (dd, J = 1.0, 8.8 Hz, 2 H, 5′-H and 8′-H), 8.82 (d, J = 4.8 Hz, 1 H, 2′-H) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 36.4 (CH_2CH_2OH), 36.9 (C-3), 55.3 (OCH_3), 60.8, 73.1, 73.5 (CH_2O), 113.9 (*C ortho* to OMe), 118.8 (C-3′), 123.0, 126.6, 129.1, 130.4 (C-5′, C-6′, C-7′, C-8′), 127.3 (C-4a′), 129.4 (*C meta* to OMe), 130.4 (CCH_2O), 148.5 (C-4′), 149.2 (C-8a′), 150.0 (C-2′), 159.4 (*C*OMe) ppm. IR: $\tilde{\nu}_{max}$ = 3416 (br), 2952, 2862, 1610, 1587, 1570, 1501, 1460, 1391, 1360, 1301, 1204, 1072, 800 cm^{-1}. GC-MS: R_t = 11.85 min. MS: m/z (%) = 337 (12.4) $[M]^+$, 336 (4.2), 276 (6.1), 156 (5.2), 154 (8.4), 121 (100.0), 77 (5.3). $C_{21}H_{23}NO_3$ (337.41): calcd. C 74.75, H 6.87, N 4.15; found C 74.8, H 6.9, N 4.1.

(*R*)-4-[(*tert*-Butyldimethylsilyl)oxy]-1-[(4-methoxybenzyl)oxy]-2-(quinolin-4-yl)butane [(*R*)-64]: This compound was prepared in 90% yield from (*R*)-**63** by the procedure reported above for the synthesis of (*R*)-**41**. Chromatography was done with PE/Et_2O 3:7 to 15:85. R_f = 0.38 (PE/Et_2O 2:8). $[a]_D$ = –10.3 (c = 1.5, $CHCl_3$). ^1H NMR (200 MHz, $CDCl_3$): δ = –0.09 and –0.07 (2×s, 2×3 H, CH_3Si), 0.85 [s, 9 H, $(CH_3)_3C$], 1.85–2.28 (m, 2 H, CH_2CH_2O), 3.42–3.77 (4 H, CH_2O), 3.79 (s, 3 H, OCH_3), 4.05 (quint., J = 6.6 Hz, 1 H, 2-H), 4.41 (s, 2 H, $ArCH_2$), 6.83 (d, J = 8.6 Hz, 2 H, *H ortho* to OMe), 7.13 (d, J = 8.6 Hz, 2 H, *H meta* to OMe), 7.32 (d, J = 4.6 Hz, 1 H, 3′-H), 7.53 (dt, J_d = 1.2, J_t = 7.6 Hz, 1 H, 6′-H), 7.71

(dt, J_d = 1.4, J_t = 7.6 Hz, 1 H, 7′-H), 8.12 (dd, J = 0.8, 8.4 Hz, 1 H, 5′-H or 8′-H), 8.18 (d, J = 9.2 Hz, 1 H, 5′-H or 8′-H), 8.84 (d, J = 4.6 Hz, 1 H, 2′-H) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = –5.5 (CH_3Si), 18.2 [$C(CH_3)_3$], 25.9 [$C(CH_3)_3$], 35.5 (CH_2CH_2OH), 35.8 (C-2), 55.2 (OCH_3), 60.6, 72.8, 72.9 (CH_2O), 113.7 (*C ortho* to OMe), 118.9 (C-3′), 123.5, 126.2, 128.9, 130.2 (C-5′, C-6′, C-7′, C-8′), 127.9 (C-4a′), 129.1 (*C meta* to OMe), 130.2 (*C*–CH_2O), 148.5 (C-4′), 149.5 (C-8a′), 150.0 (C-2′), 159.2 (*C*OMe) ppm. IR: $\tilde{\nu}_{max}$ = 2951, 2927, 2855, 1610, 1588, 1571, 1505, 1462, 1386, 1360, 1300, 1193, 1091 cm^{-1}. GC-MS: R_t = 13.13 min. MS: *m*/*z* (%) = 451 (0.04) [M]$^+$, 436 (0.1), 394 (2.5), 242 (1.6), 168 (1.8), 167 (1.6), 154 (2.0), 121 (100.0), 77 (2.7), 73 (2.8). $C_{27}H_{37}NO_3Si$ (451.67): calcd. C 71.80, H 8.26, N 3.10; found C 72.0, H 8.4, N 3.05.

Phenyl (2*R*)- and (2*S*)-4-{(*S*)-4-Acetoxy-1-[(*tert*-butyldimethylsilyl)oxy]but-2-yl}-2-[(trimethylsilyl)ethynyl]-1,2-dihydroquinoline-1-carboxylates (66a and 66b): A solution of trimethylsilylacetylene (685 μL, 4.95 mmol) in dry THF (7.6 mL) was cooled to 0 °C and treated with EtMgBr in Et_2O (3 M, 1.65 mL, 4.95 mmol). In another flask, crude quinoline (*S*)-**61** (616.6 mg, 1.65 mmol) was dissolved in dry THF (9 mL), cooled to – 78 °C and treated with the solution of trimethylsilylethynylmagnesium bromide. After 1 min, phenyl chloroformate (625 μL, 4.95 mmol) was added. The mixture was stirred at –78 °C for 1.3 h and the temperature was then allowed to rise to –30 °C over 1 h. The mixture was then poured into saturated aqueous NH_4Cl and extracted with Et_2O. The organic extracts were washed with NaOH (to remove phenol) and then with brine. After concentration, the crude product was treated with a few drops of Et_3N and immediately chromatographed with PE/AcOEt 8:2 containing Et_3N (0.5%) to give **66a** (757 mg), mixed fractions of **66a** and **66b** (190 mg) and pure **66b** (92 mg). The mixed fractions were chromatographed again, this time with PE/Et_2O 7:3, to give **66a** (112 mg) and **66b** (78 mg).

Although **66b** was analytically pure, **66a** was contaminated with diphenyl carbonate (12.5%). Full analytical characterisation of this epimer was therefore performed only after conversion into (2*R*,2′*S*)-**69a**. The calculated overall yield was 95%, whereas the diastereoisomeric ratio (GC) was 82:18 (**66a** prevailing).

Compound (2*R*,2′*S*)-66a: R_f = 0.47 (PE/Et_2O 8:2). ^{1}H NMR (200 MHz, $CDCl_3$): δ = 0.00 [s, 9 H, (CH_3)$_3$Si], 0.07 [s, 9 H, (CH_3)$_2$Si], 0.84 [s, 9 H, (CH_3)$_3$C], 1.89–2.10 (m, 1 H, C*H*HCH$_2$OAc), 2.10 (s, 3 H, CH_3CO), 2.15–2.34 (m, 1 H, C*H*HCH$_2$OAc), 3.13 (centre of m, 1 H, 2′-H), 3.55 and 3.71 (AB part of an ABX syst., J_{AB} = 9.9, J_{AX} = 6.7, J_{BX} = 4.5 Hz, 2 H, CH_2OSi), 4.09–4.41 (m, 2 H, CH_2OAc), 5.96 and 5.99 (AB syst., J = 6.6 Hz, 2 H, 2-H and 3-H), 7.18–7.53 (m, 8 H), 7.78 (br. d, J = 7.8 Hz, 1 H, 5-H or 8-H) ppm. GC-MS: R_t = 13.81 min. MS: *m*/*z* (%) = 534 [M – 57]$^+$ (12.2), 514 (4.0), 400 (3.7), 346 (25.2), 278 (6.1), 206 (5.9), 180 (6.7), 151 (13.8), 147 (5.2), 117 (48.0), 115 (5.3), 89 (22.2), 77 (15.5), 75 (37.0), 73 (100.0), 59 (6.6), 57 (5.3), 43 (22.4).

Compound (2*S*,4′*S*)-66b: R_f = 0.40 (PE/Et_2O 8:2). $[\alpha]_D$ = –220.6 (*c* = 1.1, $CHCl_3$). ^{1}H NMR (200 MHz, $CDCl_3$): δ = 0.06 [s, 9 H, (CH_3)$_3$Si], 0.08 and 0.10 [2 × s, 2 × 3 H, (CH_3)$_2$Si], 0.94 [s, 9 H, (CH_3)$_3$C], 1.78–2.04 (m, 1 H, C*H*HCH$_2$OAc), 1.99 (s, 3 H, CH_3CO), 2.00–2.20 (m, 1 H, C*H*HCH$_2$OAc), 3.07 (quint., J = 6.3 Hz, 1 H, 2′-H), 3.78 and 3.88 (AB part of an ABX syst., J_{AB} = 9.9, J_{AX} = 6.0, J_{BX} = 5.4 Hz, 2 H, CH_2OSi), 3.99–4.21 (m, 2 H, CH_2OAc), 5.98 and 6.00 (AB syst., J = 6.5 Hz, 2 H, 2-H and 3-H), 7.18–7.51 (m, 8 H), 7.77 (br. d, J = 7.4 Hz, 1 H, 5-H or 8-H) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = –5.4, –0.2 (CH_3Si), 18.2 [$C(CH_3)_3$], 20.9 (CH_3CO), 25.9 [(CH_3)$_3$C], 30.6 (CH_2CH_2OAc), 38.7 ($CHCH_2CH_2O$), 44.8 (*C*HN), 62.7, 65.8 (CH_2O), 88.5, 101.3 (*C*≡*C*) 121.6 (×3), 123.1, 124.9 (×2), 125.7, 127.6, 129.4 (×2, aromatic and olefinic *C*H), 128.3, 134.2, 136.2, 151.0 (quat.), 151.9, 170.9 (*C*=O) ppm. IR: $\tilde{\nu}_{max}$ = 3003, 2953, 2892, 2854, 1721, 1594, 1483, 1379, 1325, 1209, 1108, 962, 836 cm^{-1}. GC-MS: R_t = 14.25 min. MS: *m*/*z* (%) = 591 (1.3) [M]$^+$, 534 (2.5), 514 (6.6), 346 (38.2), 206 (4.7), 180 (6.8), 155 (7.2), 151 (10.1), 117 (37.6), 89 (22.5), 77 (17.4), 75 (39.4), 73 (100.0), 59 (7.4), 57 (5.9), 43 (27.5). $C_{33}H_{45}NO_5Si_2$ (591.89): calcd. C 66.96, H 7.66, N 2.37; found C 70.0, H 7.7, N 2.35.

Phenyl (2*S*)- and (2*R*)-4-{(*R*)-4-[(*tert*-Butyldimethylsilyl)oxy]-1-[(4-methoxybenzyl)oxy]but-2-yl}-2-[(trimethylsilyl)ethynyl]-1,2-dihydroquinoline-1-carboxylates (67a and 67b): These compounds were prepared from (*R*)-**64** (546.3 mg) by the procedure described above for **66a** and **66b**. Chromatography (PE/Et_2O 9:1 to 75:25) afforded pure **67a** (545.3 mg), pure **67b** (180.6 mg) and mixed fractions (41.2 mg). The overall yield was 93%. The diastereoisomeric ratio, determined by ^{1}H NMR on the crude product, was 73:27 (**67a** prevailing).

Compound (2*S*,2′*R*)-67a: R_f = 0.58 (PE/Et_2O 8:2). $[\alpha]_D$ = –89.7 (*c* = 1.1, $CHCl_3$). ^{1}H NMR (200 MHz, $CDCl_3$): δ = 0.03 [s, 9 H, (CH_3)$_3$Si], 0.03 and 0.04 [2 × s, 2 × 3 H, (CH_3)$_2$Si], 0.92 [s, 9 H, (CH_3)$_3$C], 1.74–1.93 (m, 1 H, C*H*HCH$_2$OSi), 1.98–2.18 (m, 1 H, C*H*HCH$_2$OSi), 3.24–3.70 (m, 3 H, CH_2OPMB and 2′-H), 3.60–3.80 (m, 2 H, CH_2OSi), 3.76 (s, 3 H, CH_3O), 4.41 (s, 2 H, ArCH_2), 5.91 and 5.94 (AB syst., J = 6.6 Hz, 2 H, 2-H and 3-H), 6.83 (d, J = 8.8 Hz, 2 H, *H ortho* to OMe), 7.10–7.43 (m, 9 H), 7.53 (dd, J = 1.0, 7.6 Hz, 1 H, 5-H or 8-H), 7.73 (br. d, J = 7.4 Hz, 1 H, 5-H or 8-H) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = –5.33, –5.27, –0.2 (CH_3Si), 18.3 [$C(CH_3)_3$], 26.0 [(CH_3)$_3$C], 34.4 (CH_2CH_2OSi), 35.4 ($CHCH_2CH_2O$), 45.0 (*C*HN), 55.2 (OCH_3), 60.5, 72.5, 73.1 (CH_2O), 88.6, 101.5 (*C*≡*C*), 113.7 (×2), 121.7 (×3), 123.4, 124.9 (×2), 125.7, 127.5, 129.0 (×2), 129.4 (×2, aromatic *C*H and H-3), 128.4, 130.4, 134.3, 136.3, 151.0, 159.1 (quat.), 151.9 (*C*=O) ppm. $C_{39}H_{51}NO_5Si_2$ (700.00): calcd. C 69.91, H 7.67, N 2.09; found C 70.2, H 7.8, N 2.0.

Compound (2*R*,4′*R*)-67b: R_f = 0.67 (PE/Et_2O 8:2). $[\alpha]_D$ = +100.4 (*c* = 1.1, $CHCl_3$). ^{1}H NMR (200 MHz, $CDCl_3$): δ = –0.06 and 0.03 [2 × s, 2 × 3 H, (CH_3)$_2$Si], 0.02 [s, 9 H, (CH_3)$_3$Si], 0.85 [s, 9 H, (CH_3)$_3$C], 1.64–1.99 (m, 2 H, CH_2CH$_2$OSi), 3.26 (quint., J = 6.3 Hz, 1 H, 2′-H), 3.50–3.72 (m, 4 H, CH_2OPMB and CH_2OSi), 3.80 (s, 3 H, CH_3O), 4.45 and 4.50 (AB syst., J = 11.6 Hz, 2 H, ArCH_2), 5.93 and 5.98 (AB syst., J = 7.0 Hz, 2 H, 2-H and 3-H), 6.86 (d, J = 8.4 Hz, 2 H, *H ortho* to OMe), 7.10–7.50 (m, 10 H), 7.72 (br. d, J = 8.0 Hz, 1 H, 5-H or 8-H) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = –5.5, –0.2 (CH_3Si), 18.2 [$C(CH_3)_3$], 25.9 [(CH_3)$_3$C], 34.7 (CH_2CH_2OSi), 36.0 ($CHCH_2CH_2O$), 44.9 (*C*HN), 55.2 (OCH_3), 60.6, 72.4, 73.0 (CH_2O), 88.5, 101.5 (*C*≡*C*), 113.7 (×2), 121.6 (×3), 123.5, 124.9 (×2), 125.7, 127.5, 129.4 (×4, aromatic *C*H and H-3), 128.2, 130.6, 134.2, 136.6, 151.0, 159.1 (quat.), 151.9 (*C*=O) ppm. $C_{39}H_{51}NO_5Si_2$ (700.00): calcd. C 69.91, H 7.67, N 2.09; found C 70.0, H 7.7, N 2.1.

Phenyl (2*R*)-4-[(*S*)-4-Hydroxy-1-(triphenylmethoxy)but-2-yl]-2-[(trimethylsilyl)ethynyl]-1,2-dihydroquinoline-1-carboxylate (68a): Compounds **65a** and **65b** were prepared from (*S*)-**59** in 79% yield and 82:18 diastereoisomeric ratio by the procedure described above for **66a** and **66b**. Chromatography gave an inseparable mixture of the two diastereoisomers. This mixture was directly subjected to Et_3Si cleavage, carried out by the same procedure as already described for the synthesis of **27a**. Chromatography (PE/Et_2O 6:4 to 1:1) gave pure **68a** in 54% yield (66% taking the starting diastereoisomeric ratio into account). Compound **68b** was not isolated. R_f = 0.60 (PE/Et_2O 4:6, R_f = of **68b** = 0.47). $[\alpha]_D$ = +218.0 (*c* = 2.1, $CHCl_3$). ^{1}H NMR (200 MHz, $CDCl_3$): δ = –0.01 [s, 9 H, (CH_3)$_3$Si], 1.87–2.06 (m, 2 H, CH_2CH$_2$O), 3.13–3.29 (m, 3 H, CH_2OTr and 2′-H),

3.68 (t, J = 6.2 Hz, 2 H CH_2OH), 5.94 (s, 2 H, 2-H and 3-H), 6.88–7.36 (m, 12 H), 7.43 (br. d, J = 8.2 Hz, 1 H, 5-H or 8-H), 7.75 (br. d, J = 7.2 Hz, 1 H, 5-H or 8-H) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = –0.3 (*C*H_3Si), 33.9 (*C*H_2CH$_2$OH), 36.2 (*C*HCH$_2$CH$_2$O), 44.9 (*C*HN), 60.7, 66.2 (*C*H_2O), 86.5 (*C*Ph$_3$), 88.8, 101.4 (*C*≡*C*) 121.7 (×2), 121.9, 123.3, 125.0, 125.1, 125.6, 126.9 (×3), 127.6, 127.7 (×6), 126.6 (×6), 129.2 (×2, aromatic and olefinic *C*H), 128.0, 134.4, 136.8, 143.9 (×3), 150.9 (quat.), 151.9 (*C*=O) ppm. IR: $\tilde{\nu}_{max}$ = 3471 (br), 3012, 2956, 1711, 1598, 1482, 1448, 1378, 1325, 1301, 1241, 1070, 1019, 962, 906, 841 cm^{-1}. $C_{44}H_{43}NO_4Si$ (677.90): calcd. C 77.96, H 6.39, N 2.07; found C 77.75, H 6.45, N 2.0.

Phenyl (2*R*)-4-[(*S*)-4-Acetoxy-1-(hydroxy)but-2-yl]-2-[(trimethylsilyl)ethynyl]-1,2-dihydroquinoline-1-carboxylate (69a): A solution of the Yamaguchi adduct (2*R*,2′*S*)-**66a** (648 mg, 87.5% pure, 0.96 mmol) in acetonitrile (6 mL) was cooled to 0 °C and treated with aqueous HF (40%, 275 μL). The solution was stirred at 0 °C for 5 h and then treated with saturated aqueous $NaHCO_3$ (20 mL) and extracted with Et_2O. After washing with brine, concentration and chromatography (PE/Et_2O 2:8 to 1:9) gave pure (2*R*,2′*S*)-**69a** (384 mg, 84%). R_f = 0.37 (PE/Et_2O 2:8). $[\alpha]_D$ = +450.8 (c = 1.37, CH_2Cl_2). ^{1}H NMR (200 MHz, $CDCl_3$): δ = 0.04 [s, 9 H, (CH_3)$_3$Si], 1.90–2.28 (m, 2 H, CH_2CH$_2$OAc), 2.07 (s, 3 H, CH_3CO), 3.16 (quint., J = 6.2 Hz, 1 H, 2′-H), 3.55–3.82 (m, 2 H, CH_2OH), 4.07–4.35 (m, 2 H, CH_2OAc), 5.94 and 6.00 (AB syst., J = 6.8 Hz, 2 H, 2-H and 3-H), 7.14–7.50 (m, 8 H), 7.77 (br. d, J = 7.6 Hz, 1 H, 5-H or 8-H) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = –0.4 (*C*H_3Si), 20.9 (*C*H_3CO), 29.5 (*C*H_2CH$_2$OAc), 38.1 (*C*HCH$_2$CH$_2$O), 44.9 (*C*HN), 62.5, 64.8 (*C*H_2O), 89.1, 100.9 (*C*≡*C*) 121.5 (×2), 122.4, 122.9, 124.9 (×2), 125.7, 127.9, 129.3 (×2, aromatic and olefinic *C*H), 127.5, 134.3, 135.2, 150.8 (quat.), 151.8, 171.0 (*C*=O) ppm. IR: $\tilde{\nu}_{max}$ = 3485 (br), 2955, 1725, 1594, 1483, 1452, 1375, 1300, 1192, 1008, 907 cm^{-1}. GC-MS: R_t = 12.59 min. MS: *m*/*z* (%) = 477 (1.8) [M]$^+$, 400 (7.5), 346 (36.4), 294 (5.1), 278 (6.2), 226 (7.4), 206 (6.4), 194 (4.9), 180 (14.5), 156 (7.9), 151 (6.9), 117 (10.5), 94 (6.2), 77 (35.3), 75 (35.1), 73 (100.0), 59 (6.3), 45 (9.5), 43 (67.5). $C_{27}H_{31}NO_5Si$ (477.62): calcd. C 67.90, H 6.54, N 2.93; found C 67.75, H 6.65, N 2.85.

Phenyl (2*R*)-4-[(*R*)-5-Acetoxy-1,1-dibromopent-1-en-3-yl]-2-trimethylsilylethynyl-1,2-dihydroquinoline-1-carboxylate (70a): This compound was prepared in 77% yield from (2*R*,2′*S*)-**69a** by the procedure described above for **47a**. Chromatography (PE/Et_2O 8:2 to 6:4) afforded pure (2*R*,3′*S*)-**70a** as an oil. R_f = 0.54 (PE/Et_2O 6:4). $[\alpha]_D$ = +230.7 (c = 2.1, $CHCl_3$). ^{1}H NMR (200 MHz, $CDCl_3$): δ = 0.06 [s, 9 H, (CH_3)$_3$Si], 1.90–2.30 (m, 2 H, CH_2CH$_2$OAc), 2.11 (s, 3 H, CH_3CO), 3.88 (dt, J_d = 5.6, J_t = 9.2 Hz, 1 H, 3′-H), 4.21 (t, J = 6.4 Hz, 2 H, CH_2OAc), 5.96 and 6.00 (AB syst., J = 6.9 Hz, 2 H, 2-H and 3-H), 6.28 (d, J = 10.0 Hz, 1 H, C*H*=CBr$_2$), 7.15–7.51 (m, 8 H), 7.76 (br. d, J = 7.8 Hz, 1 H, 5-H or 8-H) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = –0.3 (*C*H_3Si), 21.1 (*C*H_3CO), 31.9 (*C*H_2CH$_2$OAc), 40.5 (*C*HCH$_2$CH$_2$O), 44.9 (*C*HN), 61.9 (*C*H_2O), 89.3, 91.4, 100.7 (*C*≡*C* and *C*Br$_2$) 121.6 (×2), 122.1, 123.3, 125.0 (×2), 125.8, 128.2, 129.4 (×2, aromatic *C*H and H-3), 126.8, 134.3, 135.4, 150.9 (quat.), 139.5 (*C*H=CBr$_2$), 151.9, 170.9 (*C*=O) ppm. IR: $\tilde{\nu}_{max}$ = 3002, 2958, 2871, 1716, 1594, 1484, 1452, 1380, 1327, 1225, 1109, 1003, 962 cm^{-1}. $C_{28}H_{29}Br_2NO_4Si$ (631.43): calcd. C 53.26, H 4.63, N 2.22; found C 53.5, H 4.8, N 2.2.

Phenyl (2*R*)-2-Ethynyl-4-[(*R*)-5-hydroxypent-1-yn-3-yl]-1,2-dihydroquinoline-1-carboxylate (50a): The dibromide (2*R*,3′*R*)-**70a** (353.6 mg, 0.56 mmol) was converted into phenyl (2*R*)-4-[(*R*)-5-acetoxypent-1-yn-3-yl]-2-(trimethylsilyl)ethynyl-1,2-dihydroquinoline-1-carboxylate by the general procedure already described for (*R*,*R*)-**48a**. This crude product, also containing the corresponding deacetylated adduct, was taken up in absolute MeOH (10 mL), cooled to 0 °C and treated with anhydrous K_2CO_3 (33 mg). After stirring at room temp. for 2 h, the solution was poured into saturated aqueous NH_4Cl (30 mL) and extracted with Et_2O. The organic extracts were washed with brine, dried (Na_2SO_4), concentrated and chromatographed (CH_2Cl_2/Et_2O 9:1) to give pure **50a** as an oil (114 mg, 57%). R_f = 0.52 (AcOEt). $[\alpha]_D$ = +282.6 (c = 1.2, $CHCl_3$). ^{1}H NMR (200 MHz, $CDCl_3$): δ = 1.89–2.23 (m, 2 H, CH_2CH$_2$O), 2.25 (d, J = 2.6 Hz, 1 H, C≡C*H*), 2.28 (d, J = 2.6 Hz, 1 H, C≡C*H*), 3.82–4.03 (m, 3 H, CH_2OH, C*H*CH$_2$CH$_2$O), 6.02 (dd, J = 2.2, 6.6 Hz, 1 H, 2-H), 6.25 (d, J = 6.6 Hz, 1 H, 3-H), 7.14–7.47 (m, 7 H), 7.62 (dd, J = 1.5, 7.7 Hz, 1 H, 5-H or 8-H), 7.77 (br. d, J = 7.4 Hz, 1 H, 5-H or 8-H) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 30.0 (*C*HCH$_2$CH$_2$O), 37.3 (*C*H$_2$CH$_2$O), 44.1 (*C*HN), 60.3 (*C*H$_2$O), 71.7, 72.1, 79.7, 84.4 (*C*≡*C*H) 121.6 (×2), 122.1 (broad), 123.5, 124.8, 125.0, 125.8, 128.2, 129.4 (×2, aromatic and olefinic *C*H), 126.2, 134.0, 135.1, 150.8 (quat.), 151.9 (*C*=O) ppm. IR: $\tilde{\nu}_{max}$ = 3320 (broad), 3303, 3004, 2954, 2882, 1714, 1593, 1484, 1453, 1380, 1328, 1302, 1261, 1161, 1136, 1024, 974, 939, 907 cm^{-1}. GC-MS: R_t = 11.31 min. MS: *m*/*z* (%) = 357 (23.6) [M]$^+$, 356 (7.7), 329 (9.3), 313 (9.3), 312 (17.0), 280 (100.0), 274 (62.6), 230 (19.7), 228 (6.9), 221 (6.3), 220 (13.3), 218 (13.4), 217 (21.6), 216 (11.7), 206 (13.5), 204 (25.3), 203 (18.6), 202 (18.5), 192 (18.4), 191 (32.3), 190 (30.5), 189 (14.4), 180 (9.4), 178 (15.1), 176 (8.7), 166 (10.2), 165 (18.3), 164 (13.1), 163 (14.1), 154 (29.9), 152 (13.4), 139 (12.4), 128 (11.0), 127 (12.0), 115 (10.5), 77 (95.0), 65 (33.7), 63 (16.2), 51 (33.7), 43 (36.9), 39 (35.1). $C_{23}H_{19}NO_3$ (357.40): calcd. C 77.29, H 5.36, N 3.92; found C 77.1, H 5.5, N 3.8.

Phenyl (2*R*)-4-[(*R*)-5-[(*tert*-Butyldimethylsilyl)oxy]pent-1-yn-3-yl]-2-ethynyl-1,2-dihydroquinoline-1-carboxylate (71a): This compound was prepared from (2*R*,3′*R*)-**50a** by the same procedure as described above for the synthesis of (*R*)-**41**. Chromatography was carried out with PE/Et_2O 9:1 to 8:2; yield 93%. R_f = 0.63 (PE/Et_2O 7:3). $[\alpha]_D$ = +244.3 (c = 1, $CHCl_3$). ^{1}H NMR (200 MHz, $CDCl_3$): δ = 0.12 (s, 3 H, CH_3Si), 0.13 (s, 3 H, CH_3Si), 0.97 [s, 9 H, (CH_3)$_3$C], 1.90 (ddt, J_d = 9.9, 13.6, J_t = 4.0 Hz, 1 H, C*H*HCH$_2$O), 2.07–2.25 (m, 1 H, C*H*HCH$_2$O), 2.247 (d, J = 2.2 Hz, 1 H, C≡C*H*), 2.252 (d, J = 2.4 Hz, 1 H, C≡C*H*), 3.76–4.03 (m, 3 H, CH_2OSi, C*H*CH$_2$CH$_2$O), 6.04 (dd, J = 2.0, 6.7 Hz, 1 H, 2-H), 6.28 (d, J = 6.7 Hz, 1 H, 3-H), 7.14–7.47 (m, 7 H), 7.68 (dd, J = 1.2, 7.8 Hz, 1 H, 5-H or 8-H), 7.78 (br. d, J = 8.0 Hz, 1 H, 5-H or 8-H) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = –5.42, –5.36 (*C*H_3Si), 18.3 [(Si–*C*CH$_3$)$_3$], 25.9 [C(*C*H$_3$)$_3$], 29.6 (*C*HCH$_2$CH$_2$O), 38.4 (*C*H$_2$CH$_2$O), 44.1 (*C*HN), 60.3 (*C*H$_2$OSi), 71.2, 71.9 (C≡*C*H) 79.8, 84.7 (*C*≡CH), 121.6 (×2), 121.9 (broad), 123.6, 124.7, 125.0, 125.8, 128.1, 129.4 (×2, aromatic and olefinic *C*H), 126.4 (broad), 134.0, 135.4, 150.9 (quat.), 151.9 (*C*=O) ppm. IR: $\tilde{\nu}_{max}$ = 3303, 3000, 2948, 2927, 2854, 1716, 1593, 1485, 1379, 1329, 1302, 1259, 1162, 1107, 977, 938 cm^{-1}. $C_{29}H_{33}NO_3Si$ (471.66): calcd. C 73.85, H 7.05, N 2.97; found C 73.6, H 7.1, N 2.8.

Phenyl (2*S*)-4-[(*S*)-5-[(*tert*-Butyldimethylsilyl)oxy]pent-1-yn-3-yl]-2-ethynyl-1,2-dihydroquinoline-1-carboxylate (71a): The dibromide (2*S*,3′*S*)-**76a** (761.6 mg, 1.08 mmol) was converted into (2*S*,3′*S*)-**77a** by the general procedure already described for (*R*,*R*)-**48a**. The product was chromatographed with PE/Et_2O 95:5 to 9:1, to give (2*S*,3′*S*)-**77a** (535 mg). ^{1}H NMR, however, showed that it was contaminated with starting material (9.5%), which could not be separated chromatographically. This compound was thus not fully characterised, but directly converted into **71a**. The mixture (0.98 mmol) was dissolved in EtOH (96%, 14.6 mL) and cooled to –15 °C. It was treated with a solution of $AgNO_3$ (333 mg, 1.96 mmol) in H_2O (1.4 mL). A precipitate suddenly formed. After 1 h at –15 °C the reaction was complete. Then a solution of KCN (376 mg,

5.77 mmol) in H_2O (2.2 mL) was added. The mixture was stirred at 0 °C for 15 min and was then diluted with H_2O (50 mL) and extracted rapidly with Et_2O. The organic extracts were immediately washed with a mixture of KH_2PO_4 (1 M, 20 mL) and brine (20 mL). Drying (Na_2SO_4), concentration and chromatography (PE/Et_2O 9:1 to 8:2) gave pure (2*S*,3′*S*)-**71a** as a foam (308.2 mg, 60% from **76a**). $[\alpha]_D$ = –108.8 (*c* = 1.7, $CHCl_3$). The optical purity was estimated to be 42%. All other analytical and spectroscopic data were identical to those of the enantiomer.

Phenyl (2*S*,3*S*,4*R*)-4-[(*R*)-5-[(*tert*-Butyldimethylsilyl)oxy]pent-1-yn-3-yl]-3,4-epoxy-2-ethynyl-2*H*-quinoline-1-carboxylate (72a): A solution of (2*R*,3′*R*)-**71a** (306.3 mg, 0.65 mmol) in dry CH_2Cl_2 (6 mL) was cooled to 0 °C, and treated with *meta*-chloroperbenzoic acid (80% purity) (288 mg, 1.33 mmol). The solution rapidly turned red, and a precipitate formed. After 1 h the temperature was raised to room temp., and the mixture was stirred at this temperature for 20 h. After the system had again been cooled to 0 °C, Me_2S (93 μL) and saturated aqueous $NaHCO_3$ (18 mL) were added. Extraction with Et_2O, washing with brine, concentration and chromatography (PE/Et_2O 8:2) gave pure **72a** as a white foam (296.9 mg, 94%). R_f = 0.57 (PE/Et_2O 7:3), 0.57 (toluene/CH_2Cl_2/Et_2O 90:5:5). $[\alpha]_D$ = +129.2 (*c* = 2, CH_2Cl_2). ^{1}H NMR (200 MHz, $CDCl_3$): δ = 0.12 (s, 3 H, CH_3Si), 0.14 (s, 3 H, CH_3Si), 0.97 [s, 9 H, (CH_3)$_3$C], 1.71 (ddt, J_d = 10.8, 13.6, J_t = 3.2 Hz, 1 H, C*H*HCH$_2$O), 2.04–2.20 (m, 1 H, C*H*HCH$_2$O), 2.19 (d, *J* = 2.6 Hz, 1 H, C≡C*H*), 2.22 (d, *J* = 2.2 Hz, 1 H, C≡C*H*), 3.80–4.03 (m, 3 H, CH_2OSi, C*H*CH$_2$CH$_2$O), 4.12 (d, 1 H, 3-H), 5.92 (t, *J* = 2.7 Hz, 1 H, 2-H), 7.05–7.44 (m, 7 H), 7.57 (br. d, *J* = 8.0 Hz, 1 H, 5-H or 8-H), 7.76 (d, *J* = 7.0 Hz, 1 H, 5-H or 8-H) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = –5.43, –5.37 (*C*H$_3$Si), 18.3 [(Si*C*CH$_3$)$_3$], 25.9 [C(*C*H$_3$)$_3$], 29.9 (*C*HCH$_2$CH$_2$O), 35.5 (*C*H$_2$CH$_2$O), 43.7 (*C*HN), 55.9 (C-4), 60.0 (*C*H$_2$OSi), 62.8 (C-3), 72.2, 74.2 (C≡*C*H) 77.4, 80.9 (*C*≡CH), 121.5 (×2), 125.7, 125.8, 127.5 (broad), 127.8, 128.6, 129.3 (×2, aromatic *C*H), 125.5 (broad), 135.3, 151.0 (quat.), 153.4 (*C*=O) ppm. IR: $\tilde{\nu}_{max}$ = 3303, 3004, 2953, 2927, 2854, 1721, 1593, 1489, 1380, 1323, 1288, 1204, 1085, 970, 915 cm^{-1}. GC-MS: R_t 13.1. *m*/*z* 472 (0.5) [M – 15]$^+$, 430 (56.4), 337 (7.4), 336 (7.0), 310 (7.0), 309 (7.9), 308 (20.2), 294 (14.3), 290 (10.5), 280 (5.5), 278 (6.0), 274 (6.0), 262 (9.1), 244 (6.1), 230 (5.2), 228 (5.7), 218 (14.7), 217 (17.3), 206 (10.2), 204 (15.0), 191 (16.1), 180 (9.1), 178 (10.6), 151 (27.7), 140 (10.2), 115 (13.6), 89 (23.8), 83 (13.3), 77 (73.4), 75 (63.4), 73 (100.0), 65 (12.1), 59 (19.9), 57 (15.6), 51 (16.7), 41 (10.2), 39 (11.5). $C_{29}H_{33}NO_4Si$ (487.66): calcd. C 71.42, H 6.82, N 2.87; found C 71.3, H 6.8, N 2.8.

Phenyl (2*R*,3*R*,4*S*)-4-[(*S*)-5-[(*tert*-Butyldimethylsilyl)oxy]pent-1-yn-3-yl]-3,4-epoxy-2-ethynyl-2*H*-quinoline-1-carboxylate (*ent*-72a): This compound was obtained from (2*S*,3′*S*)-**71a** by the same procedure as described above for its enantiomer. $[\alpha]_D$ = –59.7 (*c* = 2, CH_2Cl_2). The optical purity was estimated to be 42%.

Phenyl (2*S*,3*S*,4*R*)-4-[(*R*)-5-[(*tert*-Butyldimethylsilyl)oxy]-1-iodopent-1-yn-3-yl]-3,4-epoxy-2-iodoethynyl-2*H*-quinoline-1-carboxylate (73a): Iodine (868 mg, 3.42 mmol) was suspended in dry benzene (15 mL) in the dark, and treated with morpholine (895 μL, 10.26 mmol). The mixture was stirred for 40 min at room temp. The resulting suspension of an orange precipitate in a relatively clear solution was treated with a solution of the diyne **72a** (277.8 mg, 570 μmol) in benzene (5 mL). After stirring for 46 h at room temp., the mixture was poured into $Na_2S_2O_3$ (0.4 M, 35 mL) and extracted three times with Et_2O (pH = 9). The organic extracts were washed in order with: a) NaH_2PO_4 (1 M, 30 mL) + citric acid (0.5 M, 7 mL, pH = 3), b) $Na_2S_2O_3$ (0.1 M, 20 mL), and c) brine. After drying (Na_2SO_4) and concentration, the crude product was immediately chromatographed (PE/Et_2O 8:2 to 7:3) to give pure **73a** as a white foam (357 mg, 85%). R_f = 0.67 (toluene/CH_2Cl_2/Et_2O 90:5:5), 0.46 (PE/Et_2O 7:3). $[\alpha]_D$ = +74.7 (*c* = 2.5, CH_2Cl_2). ^{1}H NMR (200 MHz, $CDCl_3$): δ = 0.13 (s, 3 H, CH_3Si), 0.14 (s, 3 H, CH_3Si), 0.97 [s, 9 H, (CH_3)$_3$C], 1.60–1.80 (m, 1 H, C*H*HCH$_2$O), 2.00–2.20 (m, 1 H, C*H*HCH$_2$O), 3.80–3.97 and 4.04–4.18 (2 m, 2 × 2 H, m, CH_2OSi, C*H*CH$_2$, 3-H), 6.04 (d, *J* = 2.8 Hz, 1 H, 2-H), 7.05–7.44 (m, 7 H), 7.57 (br. d, *J* = 7.6 Hz, 1 H, 5-H or 8-H), 7.70 (d, *J* = 7.8 Hz, 1 H, 5-H or 8-H) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = –5.4, –5.3 (*C*H$_3$Si), 14.1, 14.3 (*C*I), 18.3 [(Si*C*CH$_3$)$_3$], 26.0 [C(*C*H$_3$)$_3$], 32.2 (*C*HCH$_2$CH$_2$O), 35.5 (*C*H$_2$CH$_2$O), 45.5 (*C*HN), 56.1 (C-4), 60.1 (*C*H$_2$OSi), 63.0 (C-3), 87.8, 91.1 (*C*≡CI), 121.5 (×2), 125.7, 125.8, 127.4, 127.7, 128.7, 129.4 (×2, aromatic *C*H), 125.3, 135.1, 151.0 (quat.), 152.9 (*C*=O) ppm. $C_{29}H_{31}I_2NO_4Si$ (739.46): calcd. C 47.10, H 4.23, N 1.89; found C 47.35, H 4.4, N 1.9.

Enediyne 74a: A solution of the diiodide **73a** (79.0 mg, 107 μmol) in dry DMF (10 mL) was degassed and put under argon. Freshly dried lithium chloride (23 mg, 543 μmol) and $Pd(PPh_3)_4$ (20 mg, 17.3 μmol) were rapidly added, and the mixture was again put under argon through a series of vacuum/Ar cycles. A solution of (*Z*)-bis(trimethylstannyl)ethylene (33 μL, 139.4 μmol) in dry DMF (10 mL) was transferred into a dropping funnel. After the diiodide solution had been warmed to 70 °C, the stannylene solution was slowly added over 1 h. After stirring at the same temperature for 1 h, the orange solution was poured into H_2O (50 mL) and extracted four times with Et_2O. The organic extracts were washed with H_2O (40 mL) and brine, dried (Na_2SO_4), concentrated to dryness and immediately chromatographed (PE/Et_2O 9:1 to 75:25) to give pure **74a** as a foam (30.7 mg, 56%). R_f = 0.52 (PE/Et_2O 70:30). A side product (the acyclic doubly stannylated enediyne, 11.2 mg) was also obtained (R_f = 0.76). $[\alpha]_D$ = +394.2 (*c* = 1.5, $CHCl_3$). ^{1}H NMR (200 MHz, $CDCl_3$): δ = 0.09 (s, 6 H, CH_3Si), 0.91 [s, 9 H, (CH_3)$_3$C], 2.30–2.55 (m, 2 H, CH_2CH$_2$O), 3.08 (dd, *J* = 6.2, 7.4 Hz, 1 H, C*H*CH$_2$CH$_2$O), 3.70–3.92 (m, 2 H, CH_2O), 3.88 (d, *J* = 2.9 Hz, 1 H, 3-H), 5.65 (dt, J_d = 9.9, J_t = 2.6 Hz, 1 H, C*H*=CH), 5.80 (dd, *J* = 0.8, 9.9 Hz, 1 H, C*H*=CH), 5.88 (dd, *J* = 1.6, 2.9 Hz, 1 H, 2-H), 7.10–7.28 (m, 4 H), 7.29–7.42 (m, 3 H), 7.55 (br. d, *J* = 7.8 Hz, 1 H, 5-H or 8-H), 7.85 (dd, *J* = 1.3, 7.9 Hz, 1 H, 5-H or 8-H) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = –5.34, –5.28 (*C*H$_3$Si), 18.3 [(Si*C*CH$_3$)$_3$], 25.9 [C(*C*H$_3$)$_3$], 33.1 (*C*H$_2$CH$_2$O), 40.0 (*C*HCH$_2$CH$_2$O), 46.0 (*C*HN), 59.5 (C-4), 61.3 (*C*H$_2$OSi), 69.8 (C-3), 88.3, 91.1, 92.0, 102.0 (*C*≡*C*), 121.3, 121.6 (×2), 125.3, 125.5, 125.8, 128.2, 129.2, 129.4 (×3, aromatic or alkenylic *C*H), 127.0, 135.7, 151.0 (quat.), 152.9 (*C*=O) ppm. IR: $\tilde{\nu}_{max}$ = 3028, 3002, 2951, 2927, 2855, 1723, 1599, 1378, 1321, 1187, 1107, 907 cm^{-1}. $C_{31}H_{33}NO_4Si$ (511.68): calcd. C 72.77, H 6.50, N 2.74; found C 72.65, H 6.55, N 2.7.

Phenyl (2*S*)-4-[(*R*)-4-[(*tert*-Butyldimethylsilyl)oxy]-1-hydroxybut-2-yl]-2-[(trimethylsilyl)ethynyl]-1,2-dihydroquinoline-1-carboxylate (75a): A solution of (2*S*,2′*R*)-**67a** (842 mg, 1.26 mmol) in CH_2Cl_2 (50 mL) was treated with aqueous KH_2PO_4 (0.1 M, 6.4 mL) and dichlorodicyanobenzoquinone (DDQ, 438 mg, 1.93 mmol). After stirring for 1 h at room temp., the reaction mixture was quenched with aqueous $NaHCO_3$ (5%) and extracted with CH_2Cl_2. Washing with brine and concentration gave a crude product, which was chromatographed (PE/Et_2O 6:4 to 4:6) to give pure (2*S*,2′*R*)-**75a** as a foam (550 mg, 80%). R_f = 0.44 (PE/Et_2O 4:6). $[\alpha]_D$ = –146.3 (*c* = 1.1, CH_2Cl_2). ^{1}H NMR (200 MHz, $CDCl_3$): δ = 0.04 [s, 9 H, (CH_3)$_3$Si], 0.08 (s, 3 H, CH_3Si), 0.10 (s, 3 H, CH_3Si), 0.94 [s, 9 H, (CH_3)$_3$C], 1.96 (q, *J* = 5.9 Hz, 2 H, CH_2CH$_2$O), 2.73 (t, *J* = 6.4 Hz, 1 H, O*H*), 3.20 (quint., *J* = 4.9 Hz, 1 H, C*H*CH$_2$CH$_2$O), 3.52–3.96 (m, 4 H, CH_2O), 5.93 and 5.96 (AB system, 2 H, 2-H and C*H*=C),

7.14–7.44 (m, 7 H), 7.51 (dd, J = 1.5, 7.7 Hz, 1 H, 5-H or 8-H), 7.76 (br. d, J = 7.4 Hz, 1 H, 5-H or 8-H) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = –5.4 [$(CH_3)_2Si$], –0.2 [$(CH_3)_3Si$], 18.3 [$(SiCCH_3)_3$], 25.9 [$C(CH_3)_3$], 34.5 (CH_2CH_2O), 39.4 ($CHCH_2CH_2O$), 45.0 (*C*HN), 61.4, 65.7 (CH_2O), 88.7, 101.3 ($C{\equiv}C$), 121.6 (×2), 121.8 (broad), 123.3, 124.9 (×2), 125.7, 127.8, 129.4 (×2, aromatic or olefinic *C*H), 127.7, 134.4, 136.2, 150.9 (quat.), 151.9 (*C*=O) ppm. IR: $\tilde{\nu}_{max}$ = 3387 (broad), 3004, 2952, 2927, 2875, 2855, 1714, 1592, 1484, 1379, 1327, 1302, 1244, 1080, 963, 837 cm^{-1}. $C_{31}H_{43}NO_4Si_2$ (549.85): calcd. C 67.72, H 7.88, N 2.55; found C 67.9, H 7.8, N 2.45.

Phenyl (2*S*)-4-[(*S*)-5-[(*tert*-Butyldimethylsilyl)oxy]-1,1-dibromopent-1-en-3-yl]-2-trimethylsilylethynyl-1,2-dihydroquinoline-1-carboxylate (76a): This compound was prepared in 75% yield from (2*S*,2′*R*)-**75a** by the procedure described above for **47a**. Chromatography (PE/Et_2O 95:5 to 85:15) afforded pure (2*S*,3′*S*)-**76a** as an oil. R_f = 0.68 (PE/Et_2O 80:20). $[\alpha]_D$ = –92.6 (c = 2.1, $CHCl_3$). ^{1}H NMR (200 MHz, $CDCl_3$): δ = 0.04 [s, 9 H, $(CH_3)_3Si$], 0.06 and 0.09 [2×s, 2×3 H, $(CH_3)_2Si$], 0.94 [s, 9 H, $(CH_3)_3CSi$], 1.77–2.14 (m, 2 H, CH_2CH_2OSi), 3.71 (t, J = 5.8 Hz, 2 H, CH_2OSi), 3.97 (dt, J_d = 9.4, J_t = 7.2 Hz, 1 H, 3′-H), 5.95 (s, 2 H, 2-H and 3-H), 6.38 (d, J = 9.8 Hz, 1 H, *CH*=CBr_2), 7.15–7.44 (m, 7 H), 7.57 (dd, J = 1.5, 8.0 Hz, 1 H, 5-H or 8-H), 7.75 (br. d, J = 7.8 Hz, 1 H, 5-H or 8-H) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = –5.4, –0.2 (CH_3Si), 18.2 [$C(CH_3)_3$], 26.0 [$(CH_3)_3C$], 36.6 (CH_2CH_2OSi), 39.9 ($CHCH_2CH_2O$), 44.9 (*C*HN), 59.9 (CH_2O), 89.0, 90.4, 101.1 ($C{\equiv}C$ and CBr_2) 121.7 (×2), 121.9, 123.6, 124.9 (×2), 125.8, 128.0, 129.4 (×2, aromatic *C*H and H-3), 127.3, 134.2, 135.9, 150.9 (quat.), 140.6 (*C*H=CBr_2), 151.9 (*C*=O) ppm. IR: $\tilde{\nu}_{max}$ = 3003, 2951, 2855, 1712, 1595, 1475, 1419, 1381, 1329, 1193, 1040, 924 cm^{-1}. $C_{32}H_{41}Br_2NO_3Si_2$ (703.65): calcd. C 54.62, H 5.87, N 1.99; found C 54.8, H 6.0, N 1.95.

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