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Homochiral isoquinolines by lipase-catalysed resolution and their diastereoselective functionalisation

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Abstract—Kinetic resolution of racemic isoquinoline alcohols and acetates has been successfully accomplished using lipases as chiral catalysts. The diastereoselective functionalisation of the isoquinoline moiety through the addition of *C*-nucleophiles to *O*-protected alcohol **9a** in the presence of phenyl chloroformate has been carried out and dihydroquinolyl alcohol derivatives with high diastereomeric excess have been prepared.

1. Introduction

Isoquinoline containing compounds and their derivatives are a family of heterocycles widely diffused in nature. Many of these molecules are chiral and bear stereocentres in the side chain of the heterocycle or on the dihydro- or tetrahydroisoquinoline nucleus.[1] The important role played by some of them in molecular recognition,[2] and the excellent results obtained in asymmetric synthesis using some of these derivatives as catalysts or chiral auxiliaries,[3–5] explains the continuous interest of many research groups in developing new strategies for the synthesis of homochiral isoquinolines and their utilisation as starting material for the preparation of more complex targets.[1]

In the last years we have been particularly active in the area of asymmetric synthesis of new heterocyclic chiral building blocks using lipases as catalysts for the resolution or asymmetrisation of suitable alcoholic substrates.[6–9] More recently, within a project aiming to synthesise new enediyne containing *N*-heterocycles, we described the synthesis of new simplified dynemicin analogues starting from four-substituted quinoline derivatives.[10]

In continuation of our studies in this field and with the aim of synthesising some isoquinoline containing enediynes, we prepared a series of racemic 3-(1-hydroxyalkyl)isoquinolines **9a**–**9h** (Scheme 1) and examined the lipase-catalysed resolution of them and of the corresponding acetates **10a**–**10h**. Some preliminary results on the stereoselective addition of *C*-nucleophiles to different protected derivatives of alcohol **9a**, induced by the stereogenic centre present on the side chain at C(3), are also reported.

2. Results and discussion

We first prepared the ethyl ester **4** (Scheme 1), following a procedure reported for the synthesis of the corresponding methyl ester.[11,‡] Many routes for transforming **4** into **9** were attempted; however, the Claisen condensation of **4** with ethyl acetate, followed by saponification, decarboxylation and, finally, reduction of ketone **6a** furnished **9a** in less than 30% yield,[12] while the one-pot reduction–addition with $LiBH_4$/MeMgBr[13] or DIBALH/MeMgBr[14] to **4** gave **9a** in just 20% and about 50% yields, respectively. Alcohols **9a**, **9b**, **9d** and **9e** were finally obtained in acceptable yields by $NaBH_4$ reduction of the corresponding ketones **6a**,

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‡ Although the reported procedure has been used only on a 0.4 mmol scale, the transformation of **3** into **4** has been successfully scaled up to 50 mmol.

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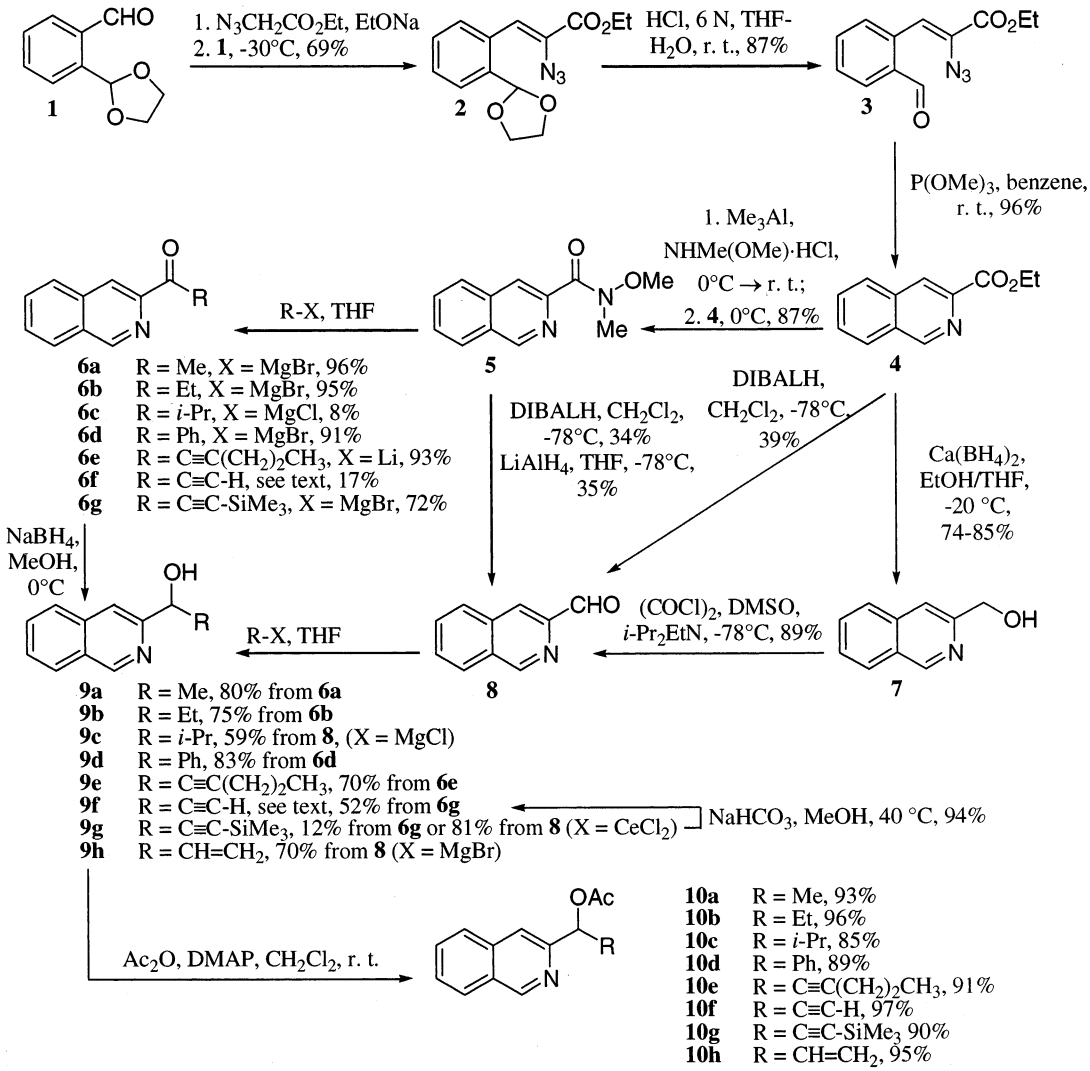


6a R = Me, X = MgBr, 96%
6b R = Et, X = MgBr, 95%
6c R = *i*-Pr, X = MgCl, 8%
6d R = Ph, X = MgBr, 91%
6e R = C≡C$(CH_2)_2CH_3$, X = Li, 93%
6f R = C≡C-H, see text, 17%
6g R = C≡C-$SiMe_3$, X = MgBr, 72%

9a R = Me, 80% from **6a**
9b R = Et, 75% from **6b**
9c R = *i*-Pr, 59% from **8**, (X = MgCl)
9d R = Ph, 83% from **6d**
9e R = C≡C$(CH_2)_2CH_3$, 70% from **6e**
9f R = C≡C-H, see text, 52% from **6g**
9g R = C≡C-$SiMe_3$, 12% from **6g** or 81% from **8** (X = $CeCl_2$)
9h R = $CH=CH_2$, 70% from **8** (X = MgBr)

10a R = Me, 93%
10b R = Et, 96%
10c R = *i*-Pr, 85%
10d R = Ph, 89%
10e R = C≡C$(CH_2)_2CH_3$, 91%
10f R = C≡C-H, 97%
10g R = C≡C-$SiMe_3$ 90%
10h R = $CH=CH_2$, 95%

Scheme 1.

6b, **6d** and **6e**,[§,¶] prepared from **4** via Weinreb's hydroxamate **5**.[19] Unfortunately this method was not satisfactory for the preparation of ketones **6c** and **6f–6h**,[‖] precursors of alcohols **9c** and **9f–9h**, which were then synthesised by the addition of the appropriate organometallics to aldehyde **8**, directly obtained by chemoselective reduction of **4** with DIBALH or of **5** with DIBALH or $LiAlH_4$.[22,23] Better results in the preparation of **8** were, however, obtained by the two-step sequence involving $Ca(BH)_4$ reduction of **4** to **7**, followed by Swern oxidation. In the case of **9g** the addition of $Me_3SiC{\equiv}CMgBr$ as well as $Me_3SiC{\equiv}CLi$ to **8** was very sluggish; on the other hand, the use of $Me_3SiC{\equiv}CCeCl_2$ allowed isolation of alcohol **9g** in very good yield.[24] The latter compound was then transformed into **9f** by mild basic treatment. All the racemic alcohols **9** where then acetylated under usual conditions to give the corresponding acetates **10**.

Encouraged by literature data concerning the kinetic resolution of different 1-pyridylethanols by means of lipase from *Candida antarctica* (CAL) using *S*-ethyl thiooctanoate as acylating agent[25] and of 1-(4-quinolyl)ethanol by means of immobilised lipase from Toyobo (LIP) using vinyl acetate as the acylating agent,[26] we examined the kinetic resolution of the alcohols **9a–9h**, using vinyl acetate as an irreversible acyl donor and different lipases either supported [lipases from *Pseudomonas cepacia* (PCL) or from porcine pancreas (PPL)] or not (CAL). We focussed our attention on the various factors affecting the reaction rate, the yield, the enantiomeric excess (e.e.) and the enantioselectivity.[**] The results are reported in Table 1.

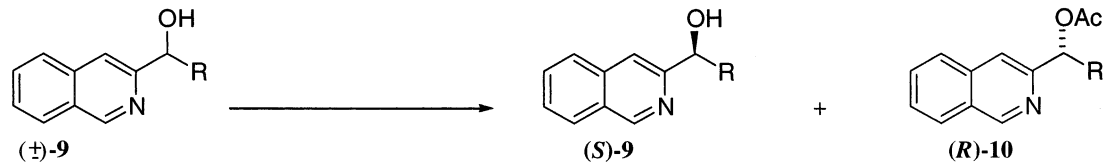
[§] Attempts to reduce ketones **6** with baker's yeast in conditions successfully used for the three isomeric acetyl pyridines failed.[15–18]

[¶] **6e** is not very stable and darkened rapidly, most likely undergoing polymerisation reactions; however, it is a suitable precursor for **9e** provided that it is immediately transformed into **6e.**

[‖] Ketone **6c** was obtained as minor product, the prevailing product being isoquinoline-3-carboxylic acid methylamide (79%) arising from basic behaviour of *i*-PrMgCl;[20,21] preparation of **6g** was also affected by *C*-desilylation as well as its reduction to the corresponding alcohol, while **6h** could not be obtained from **5** by treatment with CH_2=CHMgBr.

[**] Recently, the resolution of racemic **9a** catalysed by CAL has been reported.[27]

Table 1. Resolution of alcohols **9a**, **9b**, **9f** and **9h** catalysed by lipases



Entry	R	Enzyme[a]	Enz./**9** (mg/mmol)	Time (min)	Temp. (°C)	Conversion[b] (%)	Yield **9** (%)	Yield **10** (%)	E.e.[c] **9** (%)	E.e.[c] **10** (%)	E[d]
1	Me **9a**	CAL	80	1327	20	44.6	52	36	86.1	>99.5	>400
2	Me **9a**	CAL	84	1380	60	50.6	46	46	>99.5	96.6	>300
3	Me **9a**	S-PPL	443	4230	20	38.8	59	41	62.3	98.0	>150
4	Me **9a**	S-PPL	500	3070	25	23.2	68	19	29.7	98.4	>150
5	Me **9a**	S-PPL	400	1784	62	43.0	55	37	74.1	97.8	>150
6	Me **9a**	S-PCL	173	2810	20	21.4	72	16	27.6	>99.5	>400
7	Me **9a**	S-PCL	173	2910	Reflux	36.7	67	32	56.4	97.4	134
8	Me **9a**	S-PCL	407	1781	62	49.3	44	42	93.8	97.0	>150
9	Et **9b**	CAL	80	2947	20	15.9	63	20	18.9	>99.5	>400
10	Et **9b**	CAL	187	1425	37	34.7	63	36	52.7	99.3	>400
11	Et **9b**	CAL	201	1800	60	47.4	44	39	88.4	98.2	>300
12	Et **9b**	S-PPL	604	2880	60	43.4	51	39	74.8	97.7	>150
13	Et **9b**	S-PCL	602	2880	60	50.5	43	43	96.9	94.9	>150
14	$CH{=}CH_2$ **9h**	CAL	187	1555	37	49.2	50	46	95.9	99.1	>400
15	$CH{=}CH_2$ **9h**	CAL	200	1800	60	50.7	45	46	>99.5	96.8	>300
16	$CH{=}CH_2$ **9h**	S-PPL	602	2880	60	23.0	71	20	28.4	95.2	54
17	$CH{=}CH_2$ **9h**	S-PCL	601	2880	60	46.4	48	42	82.5	95.5	112
18	C≡CH **9f**	CAL	204	1800	60	51.8	41	49	99.2	92.3	136
19	C≡CH **9f**	S-PPL	600	2880	60	7.0	68	10	4.1	54.0	3.5
20	C≡CH **9f**	S-PCL	600	2880	60	44.1	47	41	69.0	87.5	31

[a] Vinyl acetate (VA) was used both as solvent and acylating agent, with the exception of entry 7 in which CH_2Cl_2 was used with the addition of 5 molar equivalents of VA; a concentration of 20 mg **9** per mL of solvent was used; S-PPL and S-PCL mean enzymes supported on Celite following the procedure reported in Ref. 29.

[b] Defined as the % of acetylated alcohol (mol); it was calculated from the following equation: conv = [0.5–% (*R*)-alcohol]/[% (*R*)-acetate–% (*R*)-alcohol].

[c] Determined by GLC using chiral columns Cyclodex-B™ (J&W) for R = Me (**9a** and **10a**) and Dmet.terBut.SBeta (mega) for R = Et and $CH{=}CH_2$ (only on the acetates **10b** and **10h**); **10f** was hydrogenated to **10b** before analysis was performed.

[d] Calculated as defined by Sih et al. (Ref. 30).

Once again we experienced an increased efficiency of PCL and PPL when immobilised on Celite.[28,29,††] Supported PPL and PCL have been prepared by immobilising 3 g of the crude enzyme on 10 g of Celite.[29] Usually the order of catalytic activity is S-PPL<S-PCL<CAL and thus, in order to achieve the same conversions, S-PPL and S-PCL required longer times and/or amounts of enzyme. However, with the exception of entries 19 and 20, the e.e.s of the acetates, at low conversions, were 92% from reactions using each of the three enzymes. On the other hand, the e.e.s of the corresponding alcohols are obviously strongly influenced by the degree of conversion, being very high only with conversions of $\geq 50\%$.

In Table 1 the enantioselectivity factors E,[30] which are more useful for the comparison of reactions with different degrees of conversion, are also reported and they are generally very high.

We found that the reaction rate is strongly influenced by the size of the R substituent: while for **9a** the resolution was fast enough at room temperature (entry 1), the reaction of **9b** was too sluggish (compare entries 1 and 9). Resolution of **9h** lies in between, which is probably a consequence of the relative size of the R group (Me<CH=CH_2<Et). The problem regarding low reaction rates was solved by performing the reactions at 60°C, which is in agreement with literature data on pyridine derivatives.[27] However, while CAL and PCL usually gave good results in terms of rate and e.e. for both **9** and **10**, PPL did not and this fact is particularly emphasised in the case of propargylic alcohol **9f**, for which only CAL is a suitable lipase (entries 18–20).

In conclusion, generally, CAL turned out to be the enzyme of choice for these resolutions, which appear to be strongly sensitive to the size of the group bonded to the stereogenic centre, as shown by the low reactivity of alcohols **9c**, **9d**, **9e** and **9g**: after stirring them for many hours in the presence of the enzyme (CAL or PCL) at 60°C they did not acetylate.[‡‡]

The determination of the e.e.s of **9** and **10** was performed using chiral GLC. While for **9a** and **10a** we found conditions for resolution of the enantiomers of both alcohol and acetate with just a single analysis, we were not as lucky with the other derivatives: **9b** and **9h** were actually successfully analysed only after isolation and acetylation to give **10b** and **10c,** respectively. Again the determination of the e.e. of **9f** and **10f** by GLC was not possible, since these compounds decomposed on the column. Acetate **10f** was then hydrogenated in the presence of $Pd/CaCO_3$ to give **10b**, which was analysed as above. The formation of **10b** was, however, always accompanied by a considerable amount of 3-propyliso-quinoline (at least 40%), arising from hydrogenolytic cleavage of benzylic C–O bond.[§§]

The determination of the absolute configuration of the optically active compounds was performed as follows. (a) For **9a** and **10a**: comparison of the sign of $[\alpha]_D$ with literature data[27] and Mosher's method.[33,34] (b) For **9b** and **10b**: Mosher's method was used. (c) For **9f**, **9h**, **10f** and **10h**: transformation into **10b** by catalytic hydrogenation and comparison of the sign of $[\alpha]_D$ and of the retention times in chiral GLC analysis. For the application of the Mosher method we prepared both diastereomeric MTPA esters starting from the same alcohol (+)-**9a** or (+)-**9b** and we compared the ^1H NMR spectra. We noticed the usual behaviour reported in the literature and, in addition, in this case the shielding anisotropic effect is also exerted by the isoquinoline ring on the methoxy group when it lies on the same part of the molecule with respect to the face of the C=O group. We found that the resolution of **9** always gave the (*S*)-alcohol and the (*R*)-acetate, whatever the employed lipase, in agreement with the usually observed trend in the lipase-catalysed resolution of secondary alcohols.[32] Again the model, proposed by Kazlauskas, for the prediction of the faster reacting enantiomer during the acylation of secondary alcohols under PCL (or lipase from *Candida rugosa* or cholesterol esterase) catalysis is followed.[35] In this case the large group is the heterocyclic ring, while the different alkyls constitute the medium sized group.

A valuable alternative to the resolution of alcohols **9** is the hydrolysis of the corresponding acetates, a complementary methodology for obtaining the enantiomeric (*R*)-alcohols and the (*S*)-acetates. We pursued this alternative methodology, using in this case PPL and PCL as received. There are indeed no advantages in employing enzymes supported on Celite when working in aqueous medium.

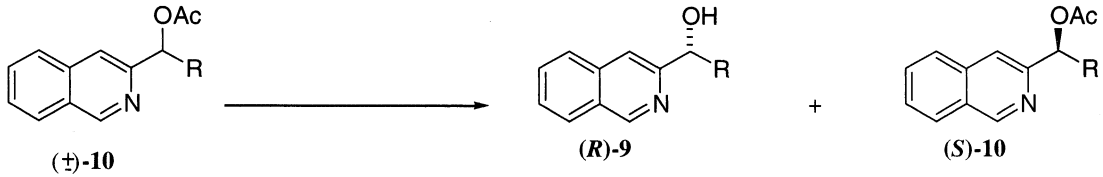
The results are collected in Table 2. With the exception of entry 1, all other reactions were performed in the presence of an organic co-solvent, which usually ensures a beneficial effect mostly on the enantioselectivity of the reaction.[36] We used three solvents with different affinities for water: *tert*-butanol, which is miscible, di-*iso*-propyl ether, which is polar but immiscible, and *n*-heptane, which is unpolar and immiscible with water. The acetates **10** are soluble only in the first two organic solvents, but insoluble in heptane. The enantioselectivity was found to be, as expected, better in the presence of the co-solvent. The reactions performed with *tert*-BuOH and *iso*-Pr_2O are similar in terms of rate and E. Using heptane, reaction rates increased for every enzyme and some reactions were even faster than in water itself (entries 1 and 3). This is an unusual result, since in most cases the presence of a co-solvent makes the reaction slower.[36] Once again CAL is clearly the best enzyme for every compound, although **10f** is not

†† Unsupported PCL did not give satisfactory results in Ref. 27.

‡‡ The influence of the size of the groups bonded to the stereogenic centre on the possibility of the alcohol to enter the catalytic site of the lipase was also experienced on other compounds.[31,32]

§§ Pd–C gave an almost exclusive hydrogenolysis reaction on **10f**.

Table 2. Resolution of alcohols **10a**, **10b**, **10f** and **10h** catalysed by lipases



Entry	R	Enzyme	Enz./**10** (mg/mmol)	Solvent[a]	Time (min)	Temp. (°C)	Conversion[b] (%)	Yield **9** (%)	Yield **10** (%)	E.e.[c] **9** (%)	E.e.[c] **10** (%)	E[d]
1	Me **10a**	CAL	80	H_2O	967	22	44.0	42	41	>99.5	78.0	>700
2	Me **10a**	CAL	80	H_2O–*t*-BuOH 85:15	1345	25	48.4	45	46	>99.5	93.3	>1000
3	Me **10a**	CAL	80	H_2O–heptane 85:15	355	23	48.2	47	40	>99.5	92.7	>1000
4	Me **10a**	CAL	84	H_2O–*i*-Pr_2O 85:15	1240	60	49.8	50	47	>99.5	98.7	>1000
5	Me **10a**	PPL	116	H_2O–*t*-BuOH 85:15	1810	26	23.2	28	68	92.8	28.8	35
6	Me **10a**	PPL	116	H_2O–*i*-Pr_2O 85:15	2415	22	34.0	32	58	98.3	45.5	>150
7	Me **10a**	PCL	133	H_2O–heptane 85:15	1200	60	43.8	44	52	>99.5	76.8	>700
8	Me **10a**	PCL	132	H_2O–*i*-Pr_2O 85:15	1620	60	45.7	46	51	>99.5	83.8	>1000
9	Et **10b**	CAL	203	H_2O–heptane 85:15	1440	60	49.9	48	43	98.7	98.3	>700
10	Et **10b**	CAL	207	H_2O–*i*-Pr_2O 85:15	1800	60	48.2	45	49	99.2	92.3	>700
11	Et **10b**	PCL	203	H_2O–heptane 85:15	1860	60	46.4	46	50	98.2	85.0	>300
12	Et **10b**	PCL	203	H_2O–*i*-Pr_2O 85:15	2340	60	48.8	45	47	98.5	93.7	>300
13	CH=CH_2 **10h**	CAL	202	H_2O–heptane 85:15	1440	60	52.5	41	39	89.7	99.2	99
14	CH=CH_2 **10h**	CAL	200	H_2O–*i*-Pr_2O 85:15	1800	60	51.4	52	43	93.4	99.1	149
15	CH=CH_2 **10h**	PCL	203	H_2O–heptane 85:15	1860	60	52.8	53	41	85.0	95.2	89
16	CH=CH_2 **10h**	PCL	199	H_2O–*i*-Pr_2O 85:15	2340	60	51.4	43	38	91.3	96.6	89
17	C≡CH **10f**	CAL	200	H_2O–heptane 85:15	1440	60	66.4	56	29	49.9	98.9	14
18	C≡CH **10f**	CAL	200	H_2O–*i*-Pr_2O 85:15	1800	60	57.7	48	38	72.5	98.9	31
19	C≡CH **10f**	PCL	200	H_2O–heptane 85:15	1860	60	65.7	50	30	51.2	98.0	13
20	C≡CH **10f**	PCL	202	H_2O–*i*-Pr_2O 85:15	2340	60	58.2	48	39	71.4	>99.5	33

[a] For reactions at $22°C \leq t \leq 26°C$ a 0.079 M phosphate buffer (pH 7) was used and the pH was maintained at 7 by continuous addition of 0.1N NaOH from an automatic burette; in the other cases a 0.33 M phosphate buffer (pH 7) was used; a concentration of 4 mg **10** per mL of solvent was used.

[b] See footnote b in Table 1.

[c] See footnote c in Table 1.

[d] See footnote d in Table 1.

an ideal substrate for lipase-catalysed hydrolysis. As in the acetylations, working at 60°C is beneficial with respect to the rate, using either CAL or PCL. It is also noteworthy that the *E* values are usually considerably higher in the hydrolysis reactions than in the acetylations. This fact makes this reaction quite attractive even if the preparation of (±)-**10** is one step longer than the preparation of the corresponding alcohols **9**.

Finally, we verified that PPL is not useful for this reaction. Even if *E* values are in some cases good (entry 6) the reactions performed at rt are too slow; by increasing the reaction temperature up to 60°C, the catalytic activity disappeared, probably due to enzyme inactivation under the employed conditions.

As experienced for the corresponding alcohols, also acetates **10c**, **10d**, **10e** and **10g** are unable to enter the catalytic site of both CAL and PCL and they were also recovered unreacted after prolonged incubation in the presence of the lipase.

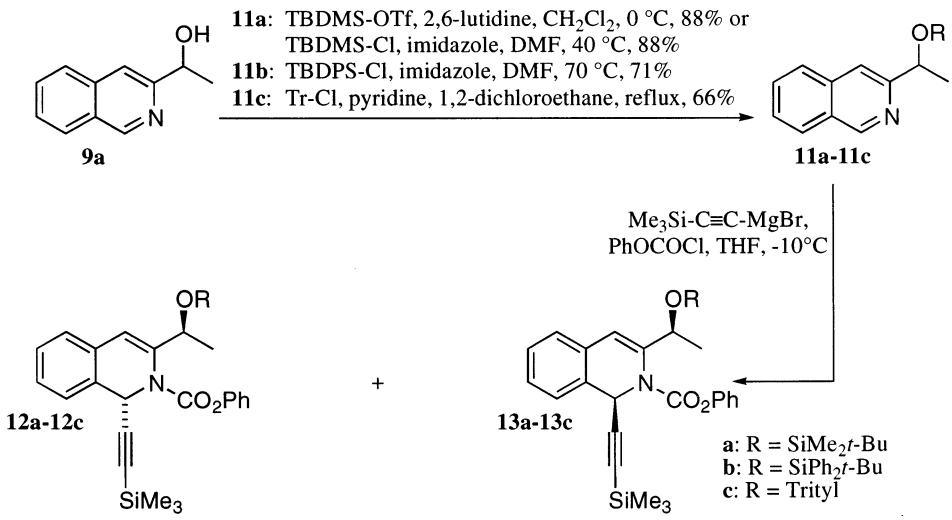
Once we had proved the possibility to obtain both enantiomers of three-substituted isoquinolines, we started to study the stereoselective functionalisation of this heterocycle. Only a few examples of diastereoselective additions to isoquinolines are known; they involve the nucleophilic addition to an *N*-acyliminium derivative of an isoquinoline with the chirality either on the acyl group,[37,38] or on the nucleophile (chiral allylsilane),[39] and addition to an *N*-iminium ion with the chirality on the exocyclic atom bonded to the nitrogen (either a stereogenic carbon[40] or a homochiral rhenium complex[41]).

In our recent project devoted to the synthesis of new enediynes, in particular to the synthesis of simplified analogues of dynemicin, a powerful anti-tumour agent,[10] we studied the diastereoselective addition of acetylides to a series of differently *O*-protected 2-(4-quinolyl)propanols, in which the stereocontrol is mostly influenced by the size of the protecting group.[42] Due to the encouraging results, we also tried to extend this protocol to isoquinoline derivatives.

In this preliminary study the reactions were carried out on (±)-**9a** but, obviously, they can be performed on the pure enantiomer of **9a** as well as on the other alcohols previously described. We protected alcohol **9a** by standard procedures to give derivatives **11a–11c** (Scheme 2), which were then submitted to the addition of magnesium trimethylsilyl acetylide in the presence of phenyl chloroformate.[42] While the TBDMS group was easily introduced, the protection as the TBDPS or trityl ethers proved troublesome, presumably due to steric reasons, which made the reactions very sluggish. The nucleophilic additions showed a different reactivity compared to our previous work on similar quinoline derivatives: while in the quinoline series the reaction was complete even at −78°C after 15–20 h, on compounds **11a–11c** it was necessary to perform the experiment at a temperature of −10°C or above in order to see the formation of new products. The regioselectivity was total and only 1-substituted-1,2-dihydroisoquinolines were detected in the reaction mixture.

In Table 3 we report the first results. For R = TBDMS and TBDPS the data are encouraging, either in terms of isolated yield or of diastereomeric ratio (entries 1 and 2), while for R = trityl the yield was modest and the diastereoselectivity was not as high as expected. However, since the diastereoselectivity does not seem to increase on introducing this large protecting group with respect to the TBDPS ether, we did not attempt to optimise the yield for both the protection and the addition reaction.

These results constitute, to the best of our knowledge, the first example of nucleophilic addition to an isoquinoline with the chirality on the substituent attached to C(3). We think that these results could be improved by extending our screening to other secondary alcohols, for example, protected **9f** and **9h**. Additionally, the presence of a multiple bond (triple in **9b** and double in **9h**) gives rise to the possibility for further synthetic



Scheme 2.

Table 3. Diastereoselective addition of Me_3Si-C≡C-MgBr to compounds **11a–11c**

Entry	Substrate	R	Yield (**12**+**13**) (%)	**12**:**13**[a]
1	**11a**	$SiMe_2t$-Bu	88	87.3:12.7[b]
2	**11b**	$SiPh_2t$-Bu	82	94.6:5.4[c]
3	**11c**	Tr	30	90.4:9.6[c]

[a] We attributed only tentatively the relative configuration to the addition products, basing our hypothesis on the results reported for quinoline derivatives (Ref. 42).
[b] Determined by GLC analysis.
[c] Determined by ^{1}H NMR analysis.

elaboration. In particular, starting from **9f**, the introduction of a second triple bond by nucleophilic addition offers the possibility to synthesise a series of new enediynes, having an isoquinoline heterocyclic system. Studies in this field are in progress in our laboratories and will be reported in due course.

3. Conclusions

We have presented the synthesis of a series of simple three-substituted isoquinolines by a common methodology. We then studied their successful kinetic resolution catalysed by lipases using both the acetylation and the hydrolysis reaction. Finally, we approached the stereoselective functionalisation of our synthons, hoping to exploit them in asymmetric synthesis and in the preparation of new compounds with potential biological activity.

4. Experimental

4.1. General

NMR spectra were taken in $CDCl_3$ (if not otherwise mentioned), at 200 MHz (^{1}H) and 50 MHz (^{13}C), using TMS as internal standard. Chemical shifts are reported in ppm (δ scale), coupling constants are reported in hertz. Peak assignment in ^{1}H NMR spectra was also made with the aid of double resonance experiments. Peak assignment in ^{13}C spectra was made with the aid of DEPT experiments. GC–MS were carried out on an HP-5971A instrument, using an HP-1 column (12 m long, 0.2 mm wide), electron impact at 70 eV and a mass temperature of about 170°C. Unless otherwise indicated analyses were performed with a constant He flow of 0.9 mL/min, init. temp. 100°C, init. time 2 min, rate 20°C/min, final temp. 260°C, final time 4 min, inj. temp. 250°C, det. temp. 280°C. IR spectra were measured with a Perkin–Elmer 881 instrument as $CHCl_3$ solutions. Values of $[\alpha]_D$ were determined on a Jasco DIP 181 polarimeter, in $CHCl_3$ (containing 0.75–1% EtOH) solution. The e.e.s of **9a** and **10a**, **10b** and **10h** were determined with an HRGC 5300 Mega Series from Carlo Erba gas chromatograph equipped with a Cyclodex-B™ (permethylated) from J&W (**9a** and **10a**) or a Dmet.terBut.SBeta (persilylated) from Mega column (**10b** and **10h**). The diastereomeric ratio of **12a** and **13a** was determined with a Fractovap from Carlo Erba gas chromatograph equipped with an SE 150 column. Melting points were determined on a Büchi 535 apparatus and are uncorrected. TLC analyses were carried out on silica gel plates, which were developed by these detection methods: (A) UV; (B) 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_fs were measured after an elution of 7–9 cm. Chromatography was carried out on 220–400 mesh silica gel using the 'flash' methodology. Petroleum ether (40–60°C) is abbreviated as PE. In extractive work-up, aqueous solutions were always re-extracted thrice with the appropriate organic solvent. Organic extracts were washed with brine, dried over Na_2SO_4 and filtered, before evaporation of the solvent under reduced pressure. All reactions employing dry solvents were carried out under a nitrogen atmosphere. The purity of all compounds was established by TLC, ^{1}H NMR and GC–MS. Lipase from recombinant *Candida antarctica* was a kind gift from Novo Nordisk. Lipase from *Pseudomonas cepacia* was kindly donated by Amano. Lipase from porcine pancreas was purchased from Sigma.

4.2. Ethyl 2-azido-3-[(2-[1,3]dioxolan-2-yl)phenyl]prop-2-enoate 2

4.2.1. Ethyl 2-azidoacetate. A solution of ethyl bromoacetate (39.4 mL, 354.9 mmol) in dry DMF (100 mL) was treated with sodium azide (46.15 g, 709.9 mmol) and stirred at 50°C for 2 h. The mixture was diluted with water and extracted with ether. The combined organic extract was washed with brine, dried and carefully concentrated under reduced pressure, without warming, to give about 70–80 mL of solution. 4 Å molecular sieves (500 mg) were added and the resulting mixture was stirred at rt for 1.5 h and used 'as is' in the next reaction. GC–MS was used to follow the reaction; in this case init. temp. 50°C and inj. temp. 100°C were used: R_t 3.54; m/z 129 (M^+, 85); 73 (23); 59 (10); 56 (89); 45 (100); 44 (21); 43 (45); 42 (81).

4.2.2. General procedure for condensation reactions. The procedure described in Ref. 11 for the corresponding methyl ester was followed, reacting **1** (15.80 g, 88.73 mmol) with the sodium enolate of the unpurified ethyl azidoacetate (4 molar equivalents). During solvent removal under reduced pressure compound **2** precipitated as a yellow solid, which after filtration and drying afforded pure **2** (16.12 g). Chromatography of the mother liquors with PE–Et_2O 9:1→65:35 afforded further **2** (1.59 g) (overall yield: 17.71 g, 69%). Mp = 63.4–63.6°C (Et_2O). R_f 0.34 (PE–Et_2O 6:4, **A**). IR: ν_{max} 3008, 2123, 1710, 1376, 1243, 1114, 1084. GC–MS: this compound decomposes in the GC column. ^{1}H NMR: 1.40 [3H, t, -CH_3, J = 7.1]; 4.11 [4H, centre of m, -OCH_2CH_2O-]; 4.38 [2H, q, -CH_2CH$_3$, J = 7.1]; 5.93 [1H, s, -OC*H*O-]; 7.34 and 7.41 [2H, 2 dt, *H meta* to -CH=CN$_3$- and *para* to -OCHO-, *H para* to -CH=CN$_3$- and *meta* to -OCHO-, J = 7.2, 2.0 and J = 8.2, 1.8]; 7.42 [1H, s, -C*H*=C]; 7.56 and 7.98 [2H, 2 dd, *H ortho* to -CH=CN$_3$-, *H ortho* to -OCHO-, J = 7.6, 2.0 and J = 7.0,

1.8]. ^{13}C NMR: 14.20 [-CH_2CH_3]; 62.25 [-OCH_2CH_3]; 65.38 [2C, -OCH_2CH_2O-]; 102.70 [-OCHO-]; 122.83 [-CH=CN_3-]; 126.67 [-CH=CN_3-]; 126.94, 128.85, 128.92 and 130.20 [4C, aromatic CH-]; 132.06 and 136.11 [2C, aromatic C]; 163.41 [CO].

4.3. Ethyl 2-azido-3-[(2-formyl)phenyl]prop-2-enoate 3

The procedure described in Ref. 11 for the corresponding methyl ester was followed. The crude product was crystallised from CH_2Cl_2–Et_2O to give a yellow solid and the resulting mother liquors were purified by chromatography, using PE–Et_2O 98:2→75:25. Compound **3** was obtained in 87% overall yield. Mp = 69.0–69.3°C (CH_2Cl_2–Et_2O). R_f 0.38 (PE–Et_2O 8:2, **A**). IR: ν_{max} 3025, 2852, 2744, 2127, 1696, 1377, 1191. GC–MS: R_t 8.25; m/z 217 (M^+−28, 100); 189 (12); 172 (21); 171 (77); 170 (14); 145 (24); 144 (13); 143 (43); 117 (5.7); 115 (16); 114 (7.2); 89 (21); 63 (6.5). ^{1}H NMR: 1.43 [3H, t, -CH_2CH_3 J = 7.7]; 4.41 [2H, q, -CH_2CH_3, J = 7.1]; 7.52 and 7.63 [2H, 2 dt, *H meta* to -CH=CN_3- and *para* to -CHO, *H para* to -CH=CN_3- and *meta* to -CHO, J = 7.5, 1.2 and J = 7.6, 1.6]; 7.69 [1H, s, -CH=CN_3-]; 7.87 and 7.93 [2H, dd and broad d, *H ortho* to -CH=CN_3-, *H ortho* to -CHO, J = 7.5, 1.5 and J = 7.5]; 10.17 [1H, s, -CHO]. ^{13}C NMR: 14.10 [-CH_2CH_3]; 62.53 [-CH_2CH_3]; 121.44 [-CH=CN_3-]; 128.73 [-CH=CN_3-]; 128.94, 130.66, 132.35 and 133.34 [4C, aromatic CH-]; 133.57 and 134.48 [2C, aromatic]; 162.94 [-CO_2Et]; 191.99 [-CHO].

4.4. Isoquinoline-3-carboxylic acid ethyl ester 4

Following the procedure reported in Ref. 11 for the corresponding methyl ester, a larger 50 mmol scale reaction was completed. The crude mixture was diluted with water and 5% aqueous Na_2CO_3 solution was added to adjust the pH of the mixture to 10. Extraction was then performed with Et_2O. Due to the propensity of **4** to undergo acid-catalysed hydrolysis of the ester function during work-up, the elimination of trimethyl phosphate was not possible by selective extraction, but only by fractional distillation under reduced pressure of crude extract to give **4** in 96% overall yield as a pale yellow oil, which solidified on standing for several hours at −25°C. Bp = 165°C/0.09 mbar (lit. 165–170°C/2 mbar[43]). R_f 0.34 (PE–Et_2O 1:9, **A**). IR: ν_{max} 2987, 1715, 1290, 1191, 1095. GC–MS: R_t 7.21; m/z 201 (M^+, 9.1); 157 (16); 156 (5.9); 130 (10); 129 (100); 128 (31); 101 (6.1). ^{1}H NMR: see Ref. 44. ^{13}C NMR: 14.15 [-CH_2CH_3]; 61.46 [-CH_2CH_3]; 123.54 [C_4]; 127.32 [C_8]; 127.61 [C_5]; 129.19 [C_7]; 129.53 [C_{8a}]; 130.78 [C_6]; 135.10 [C_{4a}]; 141.53 [C_3]; 152.34 [C_1]; 165.43 [CO].

4.5. *N*-Methyl-*N*-methoxyisoquinoline-3-carboxyamide 5

4.5.1. Preparation of MeAl(Cl)N(Me)OMe. A suspension of *N*,*O*-dimethylhydroxylamine (1.45 g, 14.91 mmol) in dry THF (15 mL) was cooled to 0°C and carefully treated with Me_3Al (2 M soln in toluene, 7.5 mL, 14.91 mmol). After methane evolution finished, the resulting pale yellow solution was stirred at rt for 30 min.

4.5.2. Reaction. The above prepared aluminium reagent was added via syringe to a solution of **4** (2.00 g, 9.94 mmol) in dry THF (8 mL), previously cooled to 0°C. After 5 min the reaction was stirred at rt for 3 h. Finally, the reaction was cooled to 0°C and quenched by cautious addition of brine, while the pH of the mixture was adjusted to 11 by addition of solid Na_2CO_3. The resulting mixture was then filtered over a Celite pad and extracted with AcOEt. The crude product was purified by chromatography with PE–AcOEt 1:1→1:9 to give **5** (1.87 g, 87% yield), which was crystallised from CH_2Cl_2–Et_2O–PE to give a white solid. Mp = 75.4–75.9°C (CH_2Cl_2–PE–Et_2O). R_f 0.40 (PE–AcOEt 3:7, **A**). IR: ν_{max} 2992, 1637, 1470, 1411, 1386, 951. GC–MS: R_t 7.93; m/z 216 (M^+, 0.02); 185 (22); 156 (26); 129 (13); 128 (100); 101 (12); 77 (12); 75 (5.5); 51 (6.0). ^{1}H NMR: 3.47 [3H, s, NCH_3]; 3.81 [3H, s, -OCH_3]; 7.69 [1H, dt, H_7, J = 6.0, 1.5]; 7.76 [1H, dt, H_6, J = 6.9, 1.6]; 7.92 [1H, broad d, H_5, J = 7.7]; 8.03 [1H, dd, H_8, J = 7.9, 1.7]; 8.14 [1H, s, H_4]; 9.25 [1H, s, H_1]. ^{13}C NMR: 34.56 [NCH_3]; 61.29 [-OCH_3]; 121.12 [C_4]; 127.29 and 127.38 [2C, C_5, C_8]; 128.44 [C_7]; 128.80 [C_{8a}]; 130.75 [C_6]; 135.47 [C_{4a}]; 146.46 [C_3]; 151.24 [C_1]; 168.71 [CO].

4.6. General procedure for the preparation of ketones 6a–6g from 5

A solution of **5** (about 5.00 mmol) in dry THF (25 mL) was cooled to −78°C. The appropriate solution of the desired organometallic reagent was then added (MeMgBr or EtMgBr, 3 M in Et_2O for **6a** and **6b**, respectively; *i*-PrMgCl, 2 M in Et_2O for **6c**; PhMgBr, 1 M in THF for **6d**; $CH_3(CH_2)_2C{\equiv}CLi$, 0.85 M in THF, obtained by treatment of 1-pentyne with *n*-BuLi, 1.6 M in hexanes at −78°C, for **6e**; TMSC≡CMgBr, 0.50 M in THF, obtained by treatment of trimethylsilylacetylene with EtMgBr, 3 M in Et_2O at 0°C, for **6f** and **6g**) and the reaction was performed at the desired temperature until complete (usually 2–5 h). The reaction temperature is reported later for each ketone. The reaction was quenched with aqueous saturated NH_4Cl solution and then extracted with Et_2O. Crude ketones were purified by chromatography with the appropriate PE–Et_2O mixtures.

4.6.1. 1-(Isoquinolin-3-yl)ethanone 6a. The temperature was allowed to rise to −40°C. Ketone **6a** was obtained in 96% yield after chromatography and was crystallised from CH_2Cl_2–Et_2O–PE to give a white solid. Mp = 88.8–89.1°C (CH_2Cl_2–Et_2O–ETP) (lit. 88°C[12]). R_f 0.37 (PE–Et_2O 6:4, **A**). IR: ν_{max} 2984, 1689, 1259. GC–MS: R_t 5.97; m/z 171 (M^+, 80); 156 (13); 143 (14); 130 (8.5); 129 (83); 128 (100); 127 (5.1); 102 (16); 101 (18); 77 (14); 76 (5.6); 75 (9.5); 51 (8.3); 43 (12). ^{1}H NMR: 2.84 [3H, s, -CH_3]; 7.70–7.83 [2H, m, H_6, H_7]; 7.97–8.09 [2H, m, H_5, H_8]; 8.50 [1H, s, H_4]; 9.30 [1H, s, H_1]. ^{13}C NMR: 26.44 [-CH_3]; 120.11 [C_4]; 127.44 and 128.50 [2C, C_5, C_8]; 129.32 [C_7]; 130.02 [C_{8a}]; 130.87 [C_6]; 135.37 [C_{4a}]; 147.60 [C_3]; 151.81 [C_1]; 200.11 [CO].

4.6.2. 1-(Isoquinolin-3-yl)propan-1-one 6b. The temperature was allowed to rise to −60°C. Ketone **6b** was

obtained in 95% yield after chromatography and was crystallised from *i*-Pr_2O–pentane to give a white solid. Mp = 56.8–57.2°C (*i*-Pr_2O–pentane) (lit. 63–64°C[45]). R_f 0.65 (PE–Et_2O 4:6, **A**). IR: ν_{max} 2980, 1689, 1168, 1132, 940, 907. GC–MS: R_t 6.31; *m*/*z* 185 (M^+, 51); 183 (17); 157 (21); 156 (22); 130 (10); 129 (89); 128 (100); 102 (7.8); 101 (13); 77 (8.0). ^{1}H NMR: 1.28 [3H, t, -CH_2CH_3, *J* = 7.2]; 3.35 [2H, q, -CH_2CH_3, *J* = 7.3]; 7.75 [2H, centre of m, H_6, H_7]; 7.97–8.06 [2H, m, H_5, H_8]; 8.48 [1H, s, H_4]; 9.28 [1H, s, H_1]. ^{13}C NMR: 8.13 [-CH_2CH_3]; 31.86 [-CH_2CH_3]; 120.10 [C_4]; 127.52 and 128.57 [2C, C_5, C_8]; 129.26 [C_7]; 130.13 [C_{8a}]; 130.90 [C_6]; 135.56 [C_{4a}]; 147.55 [C_3]; 151.83 [C_1]; 202.73 [CO].

4.6.3. 1-(Isoquinolin-3-yl)-2-methylpropan-1-one 6c. The temperature was allowed to rise to +10°C. Ketone **6c** was obtained in 8% yield after chromatography as a colourless oil. R_f 0.39 (PE–Et_2O 8:2, **A**). GC–MS: R_t 6.53; *m*/*z* 199 (M^+, 28); 198 (11); 184 (7.8); 171 (5.2); 156 (16); 143 (5.1); 130 (9.4); 129 (78); 128 (100); 102 (11); 101 (16); 77 (16); 75 (7.3); 51 (7.5); 43 (5.1); 41 (6.3); 39 (5.3). ^{1}H NMR: see Ref. 46.

4.6.4. (Isoquinolin-3-yl)phenylmethanone 6d. The temperature was allowed to rise to 0°C. Ketone **6d** was obtained in 91% yield after chromatography and was crystallised from Et_2O–PE to give a white solid. Mp = 81.5–81.8°C (Et_2O–PE) (lit. 82°C[47]). R_f 0.31 (PE–Et_2O 7:3, **A**). IR: ν_{max} 2989, 1660, 1283, 1193, 934. GC–MS: R_t 9.13; *m*/*z* 233 (M^+, 46); 232 (49); 206 (6.8); 205 (49); 204 (100); 128 (15); 105 (31); 102 (5.5); 101 (10); 77 (70); 76 (5.9); 75 (7.1); 51 (20); 50 (6.3). ^{1}H NMR: see Ref. 44. ^{13}C NMR: 123.44 [C_4]; 127.63 and 128.17 [2C, C_5, C_8]; 128.12 [2C, *C meta* of Ph]; 129.43 [C_7]; 129.56 [C_{8a}]; 130.88 [2C, *C ortho* of Ph]; 131.06 [C_6]; 132.64 [*C para* of Ph]; 135.61 [C_{4a}]; 137.01 [*C ipso* of Ph]; 148.87 [C_3]; 151.61 [C_1]; 194.33 [CO].

4.6.5. 1-(Isoquinolin-3-yl)hex-2-yn-1-one 6e. The temperature was allowed to rise to −40°C. Ketone **6e** was obtained in 93% yield after chromatography as an orange oil. R_f 0.44 (PE–Et_2O 2:3, **A**, **B**). IR: ν_{max} 2962, 2214, 1646, 1621, 1285. GC–MS: R_t 8.49; *m*/*z* 223 (M^+, 2.8); 222 (7.8); 208 (5.3); 196 (14); 195 (100); 194 (11); 180 (9.2); 167 (31); 166 (18); 156 (8.7); 140 (7.4); 139 (15); 129 (7.5); 128 (41); 102 (7.0); 101 (14); 95 (5.0); 77 (17); 76 (5.4); 75 (10); 63 (6.3); 53 (17); 51 (13); 50 (5.5); 41 (12); 39 (14). ^{1}H NMR: 1.09 [3H, t, -CH_2CH_3, *J* = 7.3]; 1.76 [2H, sextuplet, -CH_2CH_3, *J* = 7.2]; 2.57 [2H, t, -C≡C-CH_2-, *J* = 7.1]; 7.80 [2H, centre of m, H_6, H_7]; 7.98–8.12 [2H, m, H_5, H_8]; 8.62 [1H, s, H_4]; 9.37 [1H, s, H_1]. ^{13}C NMR: 13.46 [-CH_2CH_3]; 21.22 and 21.31 [2C, -$CH_2CH_2CH_3$]; 80.72 [-CO-C≡C-]; 98.36 [-CO-C≡C-]; 123.21 [C_4]; 127.56 and 128.30 [2C, C_5, C_8]; 129.88 [C_7]; 129.96 [C_{8a}]; 131.11 [C_6]; 135.04 [C_{4a}]; 147.08 [C_3]; 152.64 [C_1]; 177.76 [CO].

4.6.6. 1-(Isoquinolin-3-yl)propynone 6f. The temperature was allowed to rise to −10°C. Compound **6f** was obtained by reaction of **5** with TMSC≡CMgBr and was isolated in 17% yield after chromatography together with 72% of **6g**. Due to its instability it was rapidly characterised and, although it was a solid, it was not crystallised. R_f 0.11 (PE–Et_2O 6:4, **A**). IR: ν_{max} 3295, 2995, 2100, 1659, 1280, 1181, 946. GC–MS: R_t 6.52; *m*/*z* 181 (M^+, 33); 154 (12); 153 (100); 152 (8.5); 128 (12); 127 (12); 126 (32); 102 (6.2); 101 (14); 77 (13); 76 (6.4); 75 (10); 53 (8.9); 51 (7.9). ^{1}H NMR: 3.64 [1H, s, -C≡C*H*]; 7.77–7.89 [2H, m, H_6, H_7]; 8.00–8.13 [2H, m, H_5, H_8]; 8.65 [1H, s, H_4]; 9.40 [1H, s, H_1]. ^{13}C NMR: 81.28 [-CO-*C*≡CH]; 82.47 [-CO-C≡*C*H]; 123.28 [C_4]; 127.70 and 128.52 [2C, C_5, C_8]; 130.27 [C_{8a}]; 130.33 and 131.40 [2C, C_6, C_7]; 135.02 [C_{4a}]; 146.50 [C_3]; 152.81 [C_1]; 177.31 [CO].

4.6.7. 1-(Isoquinolin-3-yl)-3-(trimethylsilyl)propynone 6g. See also Section 4.6.6. This compound was crystallised from *i*-Pr_2O–PE to give a pale yellow solid. Mp = 73.7–74.0°C (*i*-Pr_2O–PE). R_f 0.33 (PE–Et_2O 6:4, **A**). IR: ν_{max} 2983, 2151, 1646, 1621, 1280, 1246, 1132, 1032, 947. GC–MS: R_t 8.25; *m*/*z* 253 (M^+, 100); 252 (47); 239 (13); 238 (62); 224 (5.9); 212 (6.2); 211 (19); 210 (93); 193 (11); 182 (11); 180 (6.8); 179 (8.7); 167 (8.2); 156 (14); 129 (5.6); 128 (33); 105 (15); 102 (5.1); 101 (16); 97 (7.2); 96 (15); 77 (16); 75 (10); 73 (13); 67 (8.5); 53 (8.4); 51 (7.2); 45 (5.7); 43 (14). ^{1}H NMR: 0.35 [9H, s, -Si(CH_3)$_3$]; 7.74–7.86 [2H, m, H_6, H_7]; 8.00–8.10 [2H, m, H_5, H_8]; 8.63 [1H, s, H_4]; 9.36 [1H, s, H_1]. ^{13}C NMR: −0.70 [3C, -Si(CH_3)$_3$]; 101.80 and 102.10 [2C, -CO-C≡C-]; 124.04 [C_4]; 127.70 and 128.46 [2C, C_5, C_8]; 130.16 and 131.24 [3C, C_6, C_7, C_{8a}]; 135.06 [C_{4a}]; 146.83 [C_3]; 152.92 [C_1]; 177.16 [CO].

4.7. (Isoquinolin-3-yl)methanol 7

A suspension of anhydrous $CaCl_2$ (1.66 g, 15.0 mmol) in dry THF (20 mL) and absolute ethanol (20 mL) was cooled to −20°C and treated with $NaBH_4$ (1.04 g, 27.5 mmol). After stirring the mixture for 20 min, a solution of **4** (1.01 g, 5.0 mmol) in THF (20 mL) was added and the mixture stirred for 45 min. Quenching was performed by careful addition of chilled saturated aqueous solution of NH_4Cl. Most of the solvent was removed in vacuo and the crude mixture was extracted with Et_2O. Chromatography with PE–AcOEt 1:9→AcOEt afforded the desired **7** in a 74–85% overall yield. Crystallisation from Et_2O–PE gave **7** as a white solid. Mp = 74.8–75.4°C (Et_2O–PE) (lit. 81°C[47]). R_f 0.26 (PE–AcOEt 2:8, **A**). IR: ν_{max} 3376, 2981, 1632, 1596, 1031, 951, 877. GC–MS: R_t 5.67; *m*/*z* 159 (M^+, 47); 158 (100); 132 (7.3); 131 (7.2); 130 (62); 129 (17); 128 (36); 104 (6.3); 103 (15); 102 (12); 101 (8.8); 77 (21); 76 (7.1); 75 (8.4); 63 (6.5); 51 (13). ^{1}H NMR: 3.64 [1H, broad s, -O*H*]; 4.93 [2H, s, -CH_2OH]; 7.55–7.74 [2H, m, H_6, H_7]; 7.67 [1H, s, H_4]; 7.82 [1H, broad d, H_5 or H_8, *J* = 8.4]; 7.98 [1H, broad d, H_5 or H_8, *J* = 8.1]; 9.23 [1H, s, H_1]. ^{13}C NMR: 64.87 [-CH_2OH]; 116.85 [C_4]; 126.43 and 126.90 [2C, C_5, C_8]; 127.54 [C_7]; 127.72 [C_{8a}]; 130.60 [C_6]; 136.34 [C_{4a}]; 151.85 [C_1]; 153.26 [C_3].

4.8. Isoquinoline-3-carbaldehyde 8

A solution of dry DMSO (2.26 mL, 31.8 mmol) in dry CH_2Cl_2 (10 mL) was stirred at rt in the presence of powdered 4 Å molecular sieves (50 mg) for 20 min.

After cooling to −78°C a solution of oxalyl chloride (2.6 M in CH_2Cl_2, 7.64 mL, 19.9 mmol) was added followed, after 10 min, by the addition of a solution of **7** (1.26 g, 7.95 mmol) in CH_2Cl_2 (15 mL). After stirring for a further 10 min, Hünig's base was added (9.65 mL, 55.6 mmol) and the reaction was stirred at −78°C overnight. Quenching was performed with saturated aqueous NH_4Cl and the mixture was extracted with Et_2O. After solvent removal, chromatography with PE–Et_2O 9:1→1:1 gave aldehyde **8** as a solid (1.11 g, 89%). Crystallisation from *i*-Pr_2O gave **8** as an ivory solid. Mp = 49.6–50.0°C (*i*-Pr_2O) (lit. 47°C[48]). R_f 0.33 (PE–Et_2O 1:1, **A**). IR: ν_{max} 2982, 2835, 1708, 1193, 1155, 913, 899. GC–MS: R_t 5.06; *m*/*z* 157 (M^+, 43); 130 (9.8); 129 (100); 128 (43); 103 (6.9); 102 (37); 101 (16); 77 (11); 76 (7.9); 75 (11); 74 (5.2); 51 (8.3); 50 (5.2). ^{1}H NMR: 7.84 [2H, centre of m, H_6, H_7]; 7.99–8.15 [2H, m, H_5, H_8]; 8.40 [1H, s, H_4]; 9.39 [1H, s, H_1]; 10.28 [1H, -C*H*O]. ^{13}C NMR: 121.63 [C_4]; 127.66 and 128.48 [2C, C_5, C_8]; 130.05 [C_7]; 130.38 [C_{8a}]; 131.28 [C_6]; 135.09 [C_{4a}]; 146.74 [C_3]; 153.09 [C_1]; 193.15 [-*C*HO].

4.9. General procedure for the preparation of racemic alcohols 9a, 9b, 9d, 9e, 9f and 9g by reduction of ketones 6a, 6b, 6d, 6e and 6g

A solution of **9** (2.92 mmol) in dry methanol (15 mL) was cooled to 0°C and treated with $NaBH_4$ (5.84 mmol). After stirring at 0°C for 15–30 min a saturated aqueous solution of NH_4Cl was cautiously added. The majority of solvent was evaporated under reduced pressure and the mixture was taken-up with water and Et_2O and extracted with the same solvent. Crude alcohols were purified by chromatography with the appropriate PE–Et_2O mixtures.

4.9.1. (±)-(1-Isoquinolin-3-yl)ethanol 9a. Yield after chromatography: 80%. Crystallisation from AcOEt–Et_2O afforded **9a** as a white solid. Mp = 105.4–105.8°C (AcOEt–Et_2O) (lit. 107–109°C[49]). R_f 0.27 (PE–Et_2O 1:9, **A**). GC–MS: R_t 6.07; *m*/*z* 173 (M^+, 4.2); 172 (5.8); 159 (11); 158 (100); 156 (12); 154 (5.7); 131 (5.4); 130 (51); 129 (16); 128 (39); 103 (10); 102 (13); 101 (8.4); 77 (17); 76 (6.4); 75 (6.7); 63 (5.3); 51 (10); 50 (5.8); 43 (6.6).^{1}H and ^{13}C NMR: see Ref. 27.

4.9.2. (±)-(1-Isoquinolin-3-yl)propan-1-ol 9b. Yield after chromatography: 75%. Crystallisation from Et_2O–PE afforded **9b** as a white solid. Mp = 89.6–89.8°C (Et_2O–PE) (lit. 85–87°C[45]). R_f 0.38 (PE–Et_2O 1:9, **A**). IR: ν_{max} 3413, 2997, 1631, 1402, 1192, 952, 885. GC–MS: R_t 6.32; *m*/*z* 187 (M^+, 3.0); 170 (5.8); 159 (42); 158 (100); 130 (15); 129 (12); 128 (4.1); 103 (7.7); 102 (9.2); 101 (5.6); 77 (13); 51 (6.3). ^{1}H NMR: 0.98 [3H, t, -CH_2CH_3, *J* = 7.4]; 1.79–2.09 [2H, m, -CH_2CH_3]; 3.73 [1H, broad s, -O*H*]; 4.83 [1H, broad t, C*H*OH, *J* = 4.8]; 7.58 [1H, ddd, H_7, *J* = 8.1, 6.8, 1.3]; 7.62 [1H, s, H_4]; 7.70 [1H, ddd, H_6, *J* = 8.1, 6.7, 1.3]; 7.82 [1H, broad d, H_5, *J* = 8.3]; 7.97 [1H, broad d, H_8, *J* = 8.1]; 9.22 [1H, s, H_1]. ^{13}C NMR: 9.74 [-CH_2CH_3]; 31.30 [-CH_2CH_3]; 74.74 [*C*HOH]; 116.36 [C_4]; 126.52 and 126.86 [2C, C_5, C_7]; 127.53 [C_8]; 127.83 [C_{8a}]; 130.52 [C_6]; 136.25 [C_{4a}]; 151.56 [C_1]; 155.77 [C_3].

4.9.3. (±)-(1-Isoquinolin-3-yl)phenylmethanol 9d. The crude product was directly crystallised from CH_2Cl_2 to give a white solid. The residue from the mother liquors was chromatographed with PE–Et_2O 3:7, and the products combined. Overall yield: 83%. Mp = 144.1–144.5°C (CH_2Cl_2). R_f 0.33 (PE–Et_2O 3:7, **A**). IR: ν_{max} 3402, 3004, 2955, 1630, 1593, 1397, 1022, 953. GC–MS: R_t 8.88; *m*/*z* 235 (M^+, 100); 234 (47); 218 (9.4); 217 (22); 216 (13); 206 (8.1); 180 (6.1); 159 (6.8); 158 (60); 130 (41); 129 (53); 128 (37); 108 (6.4); 103 (6.8); 102 (14); 101 (7.0); 77 (22). ^{1}H NMR: 4.80 [1H, broad s, -O*H*]; 5.96 [1H, s, C*H*OH]; 7.23–7.70 [7H, m, H_6, H_7 and Ph]; 7.56 [1H, s, H_4]; 7.75 [1H, broad d, H_5, *J* = 7.6]; 7.95 [1H, broad d, H_8, *J* = 7.8]; 9.21 [1H, s, H_1]. ^{13}C NMR: 75.46 [*C*HOH]; 117.24 [C_4]; 126.70, 127.16 and 127.63 [3C, C_5, C_7, C_8]; 127.03 [2C, *C ortho* of Ph]; 127.71 [*C para* of Ph]; 127.93 [C_{8a}]; 128.52 [2C, *C meta* of Ph]; 130.70 [C_6]; 136.36 [C_{4a}]; 143.46 [*C ipso* of Ph]; 151.50 [C_1]; 154.86 [C_3].

4.9.4. (±)-(1-Isoquinolin-3-yl)hex-2-yn-1-ol 9e. Yield after chromatography: 70% (orange oil). R_f 0.33 (PE–Et_2O 3:7, **A**, **B**). IR: ν_{max} 3375, 2960, 2931, 2225, 1630, 1387, 1140, 952. GC–MS: R_t 8.22; *m*/*z* 225 (M^+, 22); 224 (19); 210 (5.3); 209 (5.7); 208 (26); 206 (5.6); 198 (10); 197 (71); 196 (54); 183 (7.9); 182 (14); 181 (17); 180 (100); 168 (20); 167 (27); 166 (6.7); 158 (5.7); 156 (11); 139 (6.5); 131 (7.3); 130 (73); 129 (61); 128 (92); 115 (5.2); 103 (12); 102 (26); 101 (19); 77 (28); 76 (11); 75 (12); 63 (9.0); 54 (5.9); 53 (5.5); 51 (16); 50 (7.1); 41 (10); 39 (16). ^{1}H NMR: 1.00 [3H, t, -$CH_2CH_2CH_3$, *J* = 7.4]; 1.59 [2H, sextuplet, -$CH_2CH_2CH_3$, *J* = 7.3]; 2.78 [2H, dt, -$CH_2CH_2CH_3$, *J* = 7.0, 2.1]; 4.40 [1H, broad s, -O*H*]; 5.69 [1H, s, C*H*OH]; 7.61 [1H, ddd, H_7, *J* = 8.2, 6.6, 1.2]; 7.72 [1H, ddd, H_6, *J* = 8.0, 6.6, 1.0]; 7.86 [1H, broad d, H_5, *J* = 8.6]; 7.90 [1H, s, H_4]; 7.99 [1H, dd, H_8, *J* = 8.0, 0.8]; 9.24 [1H, s, H_1]. ^{13}C NMR: 13.51 [-$CH_2CH_2CH_3$]; 20.86 [-$CH_2CH_2CH_3$]; 21.96 [-$CH_2CH_2CH_3$]; 64.48 [*C*H-C≡C-]; 79.68 [CH-*C*≡C-]; 87.13 [CH-C≡*C*-]; 116.87 [C_4]; 126.84, 127.36 and 127.62 [3C, C_5, C_7, C_8]; 128.12 [C_{8a}]; 130.75 [C_6]; 136.42 [C_{4a}]; 151.90 [C_1]; 152.50 [C_3].

4.9.5. (±)-(1-Isoquinolin-3-yl)prop-2-yn-1-ol 9f. This compound was obtained in 52% yield (after chromatography) from the reduction of **6g**. Crystallisation from CH_2Cl_2–Et_2O–PE afforded **9f** as a pale yellow solid. Mp = 119.2–119.8°C (CH_2Cl_2–Et_2O–PE). R_f 0.29 (PE–Et_2O 3:7, **A**, **B**). IR: ν_{max} 3356, 3303, 2989, 2115, 1631, 1387, 1039. GC–MS: R_t 6.47; *m*/*z* 183 (M^+, 74); 182 (34); 164 (5.1); 155 (11); 154 (50); 139 (7.8); 131 (8.8); 130 (92); 129 (100); 128 (72); 127 (17); 103 (12); 102 (27); 101 (22); 77 (34); 76 (13); 75 (17); 74 (8.7); 64 (6.5); 63 (15); 62 (7.1); 55 (7.0); 53 (9.8); 51 (22); 50 (13); 39 (8.1). ^{1}H NMR: 2.68 [1H, d, -C≡C*H*, *J* = 2.2]; 5.03 [1H, broad s, -O*H*]; 5.72 [1H, d, C*H*OH, J = 2.2]; 7.62 [1H, ddd, H_7, *J* = 8.0, 6.8, 1.4]; 7.73 [1H, ddd, H_6, *J* = 8.0, 7.0, 1.4]; 7.86 [1H, d, H_5, *J* = 8.0]; 7.92 [1H, s, H_4]; 7.98 [1H, dd, H_8, *J* = 8.0, 0.8]; 9.24 [1H, s, H_1]. ^{13}C NMR: 64.05 [*C*HOH]; 74.34 [-C≡*C*H]; 83.40 [-*C*≡CH]; 117.23 [C_4]; 126.75, 127.48 and 127.53 [3C, C_5, C_7, C_8]; 127.96 [C_{8a}]; 130.85 [C_6]; 136.27 [C_{4a}]; 151.58 [C_3]; 152.03 [C_1].

4.9.6. (±)-(1-Isoquinolin-3-yl)-3-(trimethylsilyl)prop-2-yn-1-ol 9g. This compound was obtained in 12% yield (after chromatography) from the reduction of **6g**. Crystallisation from Et_2O–PE afforded **9g** as a white solid. Mp = 118.7–119.3°C (Et_2O–PE). R_f 0.54 (PE–Et_2O 3:7, **A**, **B**). IR: ν_{max} 2971, 2171, 1631, 1108, 1062, 843. GC–MS: R_t 7.94; m/z 255 (M^+, 68); 241 (13); 240 (65); 239 (20); 212 (10); 196 (11); 184 (10); 183 (73); 182 (50); 181 (98); 180 (68); 166 (14); 156 (22); 154 (13); 152 (13); 140 (13); 139 (11); 131 (11); 130 (100); 129 (96); 128 (69); 120 (15); 103 (14); 102 (24); 101 (20); 83 (29); 77 (31); 76 (10); 75 (32); 73 (54); 67 (11); 61 (10); 55 (15); 53 (16); 51 (13); 45 (39); 43 (34). ^{1}H NMR: 0.21 [9H, s, -Si(CH_3)$_3$]; 4.54 [1H, broad s, -OH]; 5.69 [1H, s, CHOH]; 7.62 [1H, ddd, H_7, J = 8.0, 7.0, 1.2]; 7.73 [1H, dt, H_6, J = 7.3, 1.2]; 7.88 [1H, d, H_5, J = 9.2]; 7.90 [1H, s, H_4]; 8.00 [1H, d, H_8, J = 8.0]; 9.23 [1H, s, H_1]. ^{13}C NMR: 0.16 [3C, -Si(CH$_3$)$_3$]; 64.68 [CHOH]; 91.15 [-C≡C-TMS]; 104.70 [-C≡C-TMS]; 117.26 [C_4]; 126.92, 127.53 and 127.67 [3C, C_5, C_7, C_8]; 128.18 [C_{8a}]; 130.88 [C_6]; 136.44 [C_{4a}]; 151.70 [C_3]; 151.94 [C_1].

4.10. General procedure for the preparation of racemic alcohols 9c and 9h from 8

A solution of **8** (5 mmol) was dissolved in dry THF (10 mL), cooled to −78°C and treated with *i*-PrMgCl (2 M in Et_2O, 1.5 molar equivalents) to give **9c** or vinylmagnesium bromide (1 M in THF, 1.5 molar equivs) to give **9h**. The temperature was then allowed to rise to −10°C over a period of about 2 h. Quenching was performed with aqueous saturated NH_4Cl and the mixture was extracted with Et_2O. Crude alcohols were purified by chromatography with the appropriate PE–Et_2O mixtures.

4.10.1. (±)-(1-Isoquinolin-3-yl)-2-methylpropan-1-ol 9c. Yield after chromatography: 59%. Crystallisation from *i*-Pr_2O–PE afforded **9c** as a pale yellow solid. Mp = 61.8–62.2°C (*i*-Pr_2O–PE). R_f 0.41 (PE–Et_2O 3:7, **A**). IR: ν_{max} 3421, 2962, 2927, 1631, 1402, 1193, 1012. GC–MS: R_t 6.66; m/z 201 (M^+, 0.96) 159 (19); 158 (100); 129 (6.9); 128 (23). ^{1}H NMR: 0.92 and 0.98 [6H, 2 d, -CH(CH_3)$_2$, J = 6.6]; 2.15 [1H, centre of m, -CH(CH$_3$)$_2$]; 3.73 [1H, broad d, -OH, J = 6.6]; 4.65 [1H, broad t, -CHOH, J = 6.1]; 7.58 [1H, s, H_4]; 7.59 [1H, dt, H_7, J = 7.3, 1.4]; 7.70 [1H, ddd, H_6, J = 8.2, 6.6, 1.2]; 7.82 [1H, d, H_5, J = 8.4]; 7.98 [1H, dd, H_8, J = 7.4, 0.8]; 9.22 [1H, s, H_1]. ^{13}C NMR: 16.74 and 19.26 [2C, -CH(CH$_3$)$_2$]; 35.02 [-CH(CH$_3$)$_2$]; 78.17 [CHOH]; 117.07 [C_4]; 126.45, 126.79 and 127.47 [3C, C_5, C_7, C_8]; 127.77 [C_{8a}]; 130.46 [C_6]; 136.02 [C_{4a}]; 151.26 [C_1]; 154.84 [C_3].

4.10.2. (±)-(1-Isoquinolin-3-yl)prop-2-en-1-ol 9h. Yield after chromatography: 70%. Crystallisation from *i*-Pr_2O–PE afforded **9h** as a pale yellow solid. Mp = 69.8–70.5°C (*i*-Pr_2O–PE). R_f 0.25 (PE–Et_2O 3:7, **A**, **B**). IR: ν_{max} 3381, 2997, 1630, 1388, 1190, 959, 927. GC–MS: R_t 6.33; m/z 185 (M^+, 9.3); 184 (7.7); 169 (14); 168 (100); 167 (13); 158 (15); 156 (13); 130 (21); 129 (46); 128 (39); 103 (8.9); 102 (17); 101 (9.7); 77 (19); 76 (6.8); 75 (7.5); 63 (6.0); 51 (11); 50 (5.6). ^{1}H NMR: 4.21 [1H, broad s, -OH]; 5.29 [1H, dt, -CH=CHH, J = 10.2, 1.3]; 5.37 [1H, broad d, CHOH, J = 6.2]; 5.50 [1H, dt, -CH=CHH, J = 16.8, 1.3]; 6.12 [1H, ddd, -CH=CH$_2$, J = 16.8, 10.4, 6.6]; 7.60 [1H, ddd, H_7, J = 8.0, 6.8, 1.4]; 7.71 [1H, ddd, H_6, J = 8.0, 7.0, 1.4]; 7.67 [1H, s, H_4]; 7.82 [1H, d, H_5, J = 8.0]; 7.99 [1H, d, H_8, J = 8.0]; 9.23 [1H, s, H_1]. ^{13}C NMR: 74.61 [CHOH]; 116.12 [-CH=CH$_2$]; 116.86 [C_4]; 126.62, 127.16 and 127.63 [3C, C_5, C_7, C_8]; 127.96 [C_{8a}]; 130.71 [C_6]; 136.40 [C_{4a}]; 139.76 [-CH=CH$_2$]; 151.65 [C_1]; 153.82 [C_3].

4.10.3. (±)-(1-Isoquinolin-3-yl)-3-(trimethylsilyl)prop-2-yn-1-ol 9g. A suspension of dry $CeCl_3$ [previously dried as described in Ref. 24 starting from $CeCl_3 \cdot 6H_2O$ (4.53 g, 12.78 mmol)] in dry THF (15 mL) was cooled, under argon, to 0°C and treated with a solution of TMS-C≡CMgBr (0.5 M) in dry THF, prepared as reported in Section 4.6. After 1 h a solution of **8** (614 mg, 3.91 mmol) in dry THF (7 mL) was added and the resulting mixture was stirred for a further 45 min at 0°C. The reaction was quenched with saturated aqueous NH_4Cl and filtered through a Celite cake, washing the residue with AcOEt. The aqueous phase was then extracted again with AcOEt. Chromatography of crude product with PE–Et_2O 6:4→9:1 afforded pure **9g** (808 mg, 81% yield). Spectroscopic data of **9g** are reported in Section 4.9.6.

4.11. (±)-(1-Isoquinolin-3-yl)prop-2-yn-1-ol 9f from 9g

A solution of **9g** (597 mg, 2.34 mmol) in dry methanol (10 mL) was treated with $NaHCO_3$ (589 mg, 7.01 mmol) and stirred at 40°C for 2.5 h. The solvent was mostly removed by distillation and the residue was partitioned between water and Et_2O and extracted. The crude product was purified by chromatography with PE–Et_2O 7:3→100% Et_2O to give **9f** (403 mg, 94% yield). Spectroscopic data of **9f** are reported in Section 4.9.5.

4.12. General procedure for the preparation of (±)-acetates 10a–10h

A solution of alcohol (1.5 mmol) in dry CH_2Cl_2 (10 mL) was treated at 0°C with acetic anhydride (3.0 mmol), triethylamine (4.5 mmol) and 4-dimethylaminopyridine (0.5 mmol). After 5 min the solution was allowed to react at rt until complete (usually about 2 h). After addition of an appropriate volume of aqueous saturated $NaHCO_3$ solution to adjust the pH of the aqueous phase at 9–10, the reaction was extracted with Et_2O and crude product was purified by chromatography with the appropriate PE–Et_2O mixtures.

4.12.1. (±)-Acetic acid 1-(isoquinolin-3-yl)ethyl ester 10a. Yield after chromatography: 93% (colourless oil). R_f 0.26 (PE–Et_2O 6:4, **A**). GC–MS: R_t 6.87; m/z 215 (M^+, 2.8); 173 (15); 172 (100); 158 (9.4); 156 (21); 154 (15); 130 (8.5); 129 (12); 128 (18); 102 (5.6); 77 (8.3); 43 (23). IR, ^{1}H and ^{13}C NMR: see Ref. 27.

4.12.2. (±)-Acetic acid 1-(isoquinolin-3-yl)propyl ester 10b. Yield after chromatography: 96% (colourless oil). R_f 0.28 (PE–Et_2O 6:4, **A**). IR: ν_{max} 2969, 2935, 1728,

1630, 1372, 1228, 1085, 1019, 960. GC–MS: R_t 6.98; m/z 229 (M^+, 0.56); 187 (5.2); 186 (35); 170 (29); 169 (49); 168 (30); 167 (7.6); 159 (14); 158 (100); 143 (11); 130 (6.4); 129 (13); 128 (27); 115 (5.4); 102 (8.6); 101 (6.5); 77 (12); 51 (5.8); 43 (47). ^{1}H NMR: 0.93 [3H, t, -CH_2CH_3, J=7.4]; 2.09 [2H, centre of m, -CH_2CH_3]; 2.16 [3H, s, -$COCH_3$]; 5.91 [1H, t, CHOAc, J=6.7]; 7.59 [1H, ddd, H_7, J=8.0, 6.8, 1.3]; 7.65 [1H, s, H_4]; 7.70 [1H, ddd, H_6, J=8.1, 6.8, 1.4]; 7.82 [1H, d, H_5, J=8.1]; 7.97 [1H, d, H_8, J=7.4]; 9.25 [1H, s, H_1]. ^{13}C NMR: 9.71 [-CH_2CH_3]; 21.20 [-$COCH_3$]; 27.65 [-CH_2CH_3]; 77.80 [CHOAc]; 117.78 [C_4]; 126.63, 127.29 and 127.46 [3C, C_5, C_6, C_7]; 127.97 [C_8]; 127.83 [C_{8a}]; 130.49 [C_6]; 136.00 [C_{4a}]; 152.32 [C_3]; 152.42 [C_1]; 170.51 [CO].

4.12.3. (±)-Acetic acid 1-(isoquinolin-3-yl)-2-methylpropyl ester 10c. Yield after chromatography: 85% (colourless oil). R_f 0.52 (PE–Et_2O 35:65, **A**). IR: ν_{max} 2961, 1727, 1631, 1371, 1238, 1018. GC–MS: R_t 7.20; m/z 243 (M^+, 0.35); 201 (5.0); 200 (6.3); 184 (12); 183 (19); 182 (20); 168 (8.6); 167 (5.5); 159 (13); 158 (100); 143 (11); 129 (8.4); 128 (18); 102 (5.1); 77 (6.8); 43 (32). ^{1}H NMR: 0.87 and 1.01 [6H, 2 d, -$CH(CH_3)_2$, J=7.0]; 2.15 [3H, s, -$COCH_3$]; 2.51 [1H, octuplet, -$CH(CH_3)_2$, J=6.9]; 5.71 [1H, d, -CHOAc, J=7.4]; 7.59 [1H, ddd, H_7, J=8.0, 6.8, 1.4]; 7.62 [1H, s, H_4]; 7.70 [1H, ddd, H_6, J=8.0, 7.0, 1.4]; 7.82 [1H, d, H_5, J=8.0]; 7.96 [1H, dd, H_8, J=8.0, 0.8]; 9.25 [1H, s, H_1]. ^{13}C NMR: 17.88 and 18.95 [2C, -$CH(CH_3)_2$]; 21.09 [-$COCH_3$]; 32.00 [$CH(CH_3)_2$]; 81.30 [CHOAc]; 118.43 [C_4]; 126.63, 127.16 and 127.44 [3C, C_5, C_7, C_8]; 127.91 [C_{8a}]; 130.45 [C_6]; 135.85 [C_{4a}]; 151.87 [C_3]; 152.31 [C_3]; 170.56 [CO].

4.12.4. (±)-Acetic acid 1-(isoquinolin-3-yl)phenylmethyl ester 10d. Yield after chromatography: 89%. Crystallisation from Et_2O–PE afforded **10d** as a white solid. Mp=75.0–75.5°C (Et_2O–PE). R_f 0.20 (PE–Et_2O 6:4, **A**). IR: ν_{max} 2969, 1741, 1630, 1371, 1237, 1019. GC–MS: R_t 9.24; m/z 277 (M^+, 6.4); 235 (20); 234 (100); 218 (30); 217 (42); 216 (15); 156 (7.6); 129 (12); 128 (42); 102 (5.8); 101 (5.7); 77 (17); 51 (8.3); 43 (34). ^{1}H NMR: 2.24 [3H, s, -$COCH_3$]; 7.07 [1H, s, CHOAc]; 7.25–7.51 [5H, m, Ph]; 7.59 [1H, ddd, H_7, J=8.0, 6.6, 1.2]; 7.70 [1H, ddd, H_6, J=8.4, 7.0, 1.4]; 7.77 [1H, s, H_4]; 7.83 [1H, d, H_5, J=8.0]; 7.95 [1H, d, H_8, J=8.0]; 9.22 [1H, s, H_1]. ^{13}C NMR: 21.28 [-$COCH_3$]; 77.76 [CHOAc]; 117.38 [C_4]; 126.70, 127.36 and 127.50 [3C, C_5, C_7, C_8]; 127.50 [2C, *C ortho* of Ph]; 127.85 [C_{8a}]; 128.07 [*C para* of Ph]; 128.47 [2C, *C meta* of Ph]; 130.59 [C_6]; 136.06 [C_{4a}]; 139.20 [*C ipso* of Ph]; 152.40 [C_3]; 152.60 [C_1]; 169.95 [CO].

4.12.5. (±)-Acetic acid 1-(isoquinolin-3-yl)hex-2-ynyl ester 10e. Yield after chromatography: 91% (orange oil). R_f 0.35 (PE–Et_2O 4:6, **A**, **B**). IR: ν_{max} 2962, 2235, 1739, 1630, 1370, 1014, 949. GC–MS: R_t 8.66; m/z 267 (M^+, 5.4); 237 (9.1); 225 (25); 224 (100); 209 (7.6); 208 (33) 206 (11); 197 (8.8); 196 (46); 195 (6.6); 193 (9.8); 192 (9.3); 182 (7.2); 181 (8.4); 180 (47); 168 (8.7); 167 (21); 166 (5.9); 156 (35); 152 (7.3); 139 (6.8); 130 (6.4); 129 (19); 128 (81); 102 (11); 101 (12); 77 (18); 76 (6.3); 75 (8.7); 63 (7.0); 51 (10); 43 (49); 39 (8.0). ^{1}H NMR: 0.99 [3H, t, -$CH_2CH_2CH_3$, J=7.4]; 1.58 [2H, sextuplet, -$CH_2CH_2CH_3$, J=7.2]; 2.16 [3H, s, -$COCH_3$]; 2.29 [2H, dt, -$CH_2CH_2CH_3$, J=6.8, 2.2]; 6.67 [1H, t, CHOAc, J=2.1]; 7.63 [1H, ddd, H_7, J=8.0, 7.0, 1.2]; 7.73 [1H, dt, H_6, J=7.0, 1.4]; 7.87 [1H, d, H_5, J=8.0]; 7.93 [1H, s, H_4]; 8.00 [1H, d, H_8, J=7.6]; 9.28 [1H, s, H_1]. ^{13}C NMR: 13.42 [-$CH_2CH_2CH_3$]; 20.82 [-C≡CCH_2-]; 21.06 [-$COCH_3$]; 21.75 [-$CH_2CH_2CH_3$]; 66.98 [CHOAc]; 76.28 [CH-C≡CH]; 88.56 [CH-C≡CH]; 118.51 [C_4]; 126.85, 127.46 and 127.68 [3C, C_5, C_7, C_8]; 128.16 [C_{8a}]; 130.63 [C_6]; 136.00 [C_{4a}]; 149.59 [C_3]; 152.70 [C_1]; 169.74 [CO].

4.12.6. (±)-Acetic acid 1-(isoquinolin-3-yl)prop-2-ynyl ester 10f. Yield after chromatography: 97% (colourless oil). R_f 0.49 (PE–Et_2O 3:7, **A**). IR: ν_{max} 3302, 3008, 2130, 1738, 1630, 1370, 1203, 1015, 946. GC–MS: R_t 7.14; m/z 225 (M^+, 2.4); 183 (35); 182 (100); 166 (11); 164 (8.1); 156 (8.4); 154 (8.0); 140 (7.1); 139 (14); 138 (5.7); 130 (5.0); 129 (16); 128 (46); 101 (5.8); 77 (6.4); 63 (8.0); 51 (5.8); 43 (6.4). ^{1}H NMR: 2.19 [3H, s, -$COCH_3$]; 2.73 [1H, d, -C≡CH, J=2.2]; 6.68 [1H, d, CHOAc, J=2.2]; 7.65 [1H, dt, H_7, J=8.0, 1.4]; 7.74 [1H, dt, H_6, J=7.0, 1.4]; 7.88 [1H, d, H_5, J=8.0]; 7.95 [1H, s, H_4]; 8.00 [1H, broad d, H_8, J=8.4]; 9.29 [1H, s, H_1]. ^{13}C NMR: 21.00 [-$COCH_3$]; 66.31 [CHOAc]; 75.69 [-C≡CH]; 79.72 [-C≡CH]; 118.90 [C_4]; 126.96, 127.60 and 128.02 [3C, C_5, C_7, C_8]; 128.37 [C_{8a}]; 130.90 [C_6]; 136.06 [C_{4a}]; 148.46 [C_3]; 152.97 [C_1]; 169.65 [CO].

4.12.7. (±)-Acetic acid 1-(isoquinolin-3-yl)-3-(trimethylsilyl)prop-2-ynyl ester 10g. Yield after chromatography: 90% (colourless oil). R_f 0.28 (PE–Et_2O 1:1, **A**). IR: ν_{max} 2962, 2232, 1742, 1629, 1368, 1251, 1229, 1048, 1017, 872. GC–MS: R_t 8.35; m/z 297 (M^+, 15); 256 (10); 255 (42); 254 (100); 240 (24); 239 (8.7); 238 (26); 236 (6.1); 211 (5.4); 208 (5.7); 196 (5.0); 182 (12); 181 (6.0); 180 (20); 156 (30); 154 (5.1); 152 (6.5); 130 (5.9); 129 (11); 128 (38); 101 (5.7); 83 (5.6); 77 (8.6); 75 (12); 73 (24); 67 (5.5); 53 (7.8); 45 (8.4); 43 (57). ^{1}H NMR: 0.20 [9H, s, -$Si(CH_3)_3$]; 2.16 [3H, s, -$COCH_3$]; 6.68 [1H, s, CHOAc]; 7.63 [1H, dt, H_7, J=7.0, 1.4]; 7.72 [1H, dt, H_6, J=7.0, 1.6]; 7.86 [1H, d, H_5, J=8.2]; 7.92 [1H, s, H_4]; 7.99 [1H, d, H_8, J=7.6]; 9.26 [1H, s, H_1]. ^{13}C NMR: –0.25 [3C, -$Si(CH_3)_3$]; 21.11 [-$COCH_3$]; 66.92 [CHOAc]; 92.91 [-C≡C-TMS]; 100.73 [-C≡C-TMS]; 118.82 [C_4]; 126.99, 127.58 and 127.86 [3C, C_5, C_7, C_8]; 128.32 [C_{8a}]; 130.75 [C_6]; 136.10 [C_{4a}]; 149.11 [C_3]; 152.83 [C_1]; 169.65 [CO].

4.12.8. (±)-Acetic acid 1-(isoquinolin-3-yl)allyl ester 10h. Yield after chromatography: 95% (pale yellow oil). R_f 0.37 (PE–Et_2O 4:6, **A**, **B**). IR: ν_{max} 2978, 1736, 1630, 1371, 1193, 938. GC–MS: R_t 7.00; m/z 227 (M^+, 2.1); 185 (8.9); 184 (55); 169 (12); 168 (100); 167 (34); 166 (7.4); 158 (7.1); 156 (10); 139 (6.9); 129 (14); 128 (29); 102 (6.1); 101 (6.8); 83 (11); 51 (10); 43 (34). ^{1}H NMR: 2.19 [3H, s, -$COCH_3$]; 5.34 [1H, dt, CH=CHH, J=10.2, 1.3]; 5.44 [1H, dt, C=CHH, J=16.8, 1.4]; 6.23 [1H, ddd, -CH=CH_2, J=16.8, 10.2, 6.2]; 6.48 [1H, d, CHOAc, J=6.2]; 7.61 [1H, ddd, H_7, J=8.0, 6.6, 1.0]; 7.71–7.75 [1H, m, H_6]; 7.72 [1H, s, H_4]; 7.84 [1H, d, H_5, J=8.0]; 7.98 [1H, d, H_8, J=8.0]; 9.27 [1H, s, H_1]. ^{13}C NMR: 21.25 [-$COCH_3$]; 77.00 [CHOAc]; 117.83 [-CH=CH_2];

118.05 [C_4]; 126.73, 127.49 and 127.55 [3C, C_5, C_7, C_8]; 128.05 [C_{8a}]; 130.65 [C_6]; 135.32 [-CH=CH_2]; 136.16 [C_{4a}]; 151.31 [C_3]; 152.64 [C_1]; 170.00 [CO].

4.13. General procedure for kinetic resolution of alcohols 9a, 9b, 9f and 9h catalysed by lipases

A solution of the desired alcohol (80 mg) in vinyl acetate (4 mL) was stirred under nitrogen for 15 min at rt in the presence of powdered 3 Å molecular sieves (8 mg). Then the lipase was added (for amounts see Table 1) and the mixture was vigorously stirred at the desired temperature for the reported time. The enzyme was removed by filtration and the solution was concentrated in vacuo and finally purified by chromatography with the appropriate PE–Et_2O mixtures (usually 4:6→1:9). Characterisation of alcohols and acetates was already reported above. (*S*)-**9a**: $[\alpha]_D=-40.4$ (*c* 1.01, $CHCl_3$), (e.e. >99.5%); (*S*)-**9b**: $[\alpha]_D=-45.2$ (*c* 1.15, $CHCl_3$), (e.e. = 96.9%); (*S*)-**9f**: $[\alpha]_D=-61.1$ (*c* 1.20, $CHCl_3$), (e.e. 99.2%); (*S*)-**9h**: $[\alpha]_D=+19.5$ (*c* 1.11, $CHCl_3$), (e.e. >99.5%); (*R*)-**10a**: $[\alpha]_D=+109.7$ (*c* 1.06, $CHCl_3$), (e.e. >99.5%); (*R*)-**10b**: $[\alpha]_D=+95.4$ (*c* 0.98, $CHCl_3$), (e.e. = 99.2%); (*R*)-**10f**: $[\alpha]_D=+32.3$ (*c* 1.49, $CHCl_3$), (e.e. = 92.3%); (*R*)-**10h**: $[\alpha]_D=+54.9$ (*c* 0.68, $CHCl_3$), (e.e. = 99.1%).

4.14. General procedure for the kinetic resolution of acetates 10a, 10b, 10f and 10h catalysed by lipases

The acetate (80 mg) was dissolved or partially dissolved into the desired organic solvent (3 mL), then the appropriate buffer solution (17 mL, see footnotes of Table 2) was added, followed by the enzyme (for amounts see Table 2) and the mixture was vigorously stirred at the reported temperature for the reported time. The mixture was then filtered over a Celite cake, washing the residue with AcOEt. The aqueous phase was saturated with NaCl and then extracted with AcOEt. Chromatography of crude product was performed with the appropriate PE–Et_2O mixtures (usually 4:6→1:9). Characterisation of alcohols and acetates was already reported above. (*R*)-**9a**: $[\alpha]_D=+45.6$ (*c* 1.00, $CHCl_3$), (e.e. >99.5%); (*R*)-**9b**: $[\alpha]_D=+49.0$ (*c* 0.98, $CHCl_3$), (e.e. = 99.2%); (*R*)-**9f**: $[\alpha]_D=$ = +47.1 (*c* 1.51, $CHCl_3$), (e.e. = 72.5%); (*R*)-**9h**: $[\alpha]_D=-14.8$ (*c* 1.11, $CHCl_3$), (e.e. = 93.4%); (*S*)-**10a**: $[\alpha]_D=-106.3$ (*c* 1.04, $CHCl_3$), (e.e. = 98.7%); (*S*)-**10b**: $[\alpha]_D=-94.0$ (*c* 1.36, $CHCl_3$), (e.e. = 98.3%); (*S*)-**10f**: $[\alpha]_D=-29.5$ (*c* 1.51, $CHCl_3$), (e.e. >99.5%); (*S*)-**10h**: $[\alpha]_D=-51.5$ (*c* 1.56, $CHCl_3$), (e.e. = 99.2%).

4.15. General procedure for the preparation of the Mosher esters (MTPA) of 9a and 9b

A solution of the desired alcohol (5 mg) in dry CH_2Cl_2 (1 mL) was treated at 0°C with 4-dimethylaminopyridine (6 molar equivalents) and the desired Mosher's chloride (3 molar equivalents). After 5 min the solution was stirred at rt until complete (about 30 min). The chromatographic purification was made on the crude solution by preparative TLC, using PE–Et_2O 6:4 as eluent, to give the corresponding esters in >90% yield.

4.15.1. (*R*)-MTPA ester of (+)-9a. R_f 0.45 (PE–Et_2O 6:4, **A**). ^{1}H NMR: 1.73 [3H, d, CHCH_3, $J=6.6$]; 3.54 [3H, centre of m, -OCH_3]; 6.35 [1H, q, CHCH_3, $J=6.6$]; 7.32–7.76 [8H, m, H of Ph, H_4, H_6, H_7]; 7.79 [1H, broad d, H_5, $J=8.8$]; 7.99 [1H, broad d, H_8, $J=8.8$]; 9.24 [1H, s, H_1].

4.15.2. (*S*)-MTPA ester of (+)-9a. R_f 0.39 (PE–Et_2O 6:4, **A**). ^{1}H NMR: 1.78 [3H, d, CHCH_3, $J=6.6$]; 3.65 [3H, centre of m, -OCH_3]; 6.35 [1H, q, CHCH_3, $J=6.6$]; 7.31–7.73 [9H, m, H of Ph, H_4, H_5, H_6, H_7]; 7.96 [1H, broad d, H_8, $J=7.9$]; 9.19 [1H, s, H_1].

4.15.3. (*R*)-MTPA ester of (+)-9b. R_f 0.49 (PE–Et_2O 6:4, **A**). ^{1}H NMR: 0.88 [3H, t, -CH_2CH_3, $J=7.6$]; 2.13 [2H, quintuplet, -CH_2CH_3, $J=7.2$]; 3.51 [3H, centre of m, -OCH_3]; 6.15 [1H, t, CHCH_2CH_3, $J=6.4$]; 7.31–7.79 [9H, m, H of Ph, H_4, H_5, H_6, H_7]; 7.99 [1H, broad d, H_8, $J=8.0$]; 9.25 [1H, s, H_1].

4.15.4. (*S*)-MTPA ester of (+)-9b. R_f 0.43 (PE–Et_2O 6:4, **A**). ^{1}H NMR: 0.99 [3H, t, -CH_2CH_3, $J=7.5$]; 2.14 [2H, centre of m, -CH_2CH_3]; 3.64 [3H, centre of m, -OCH_3]; 6.15 [1H, t, CHCH_2CH_3, $J=6.4$]; 7.28–7.73 [9H, m, H of Ph, H_4, H_5, H_6, H_7]; 7.96 [1H, broad d, H_8, $J=8.0$]; 9.18 [1H, s, H_1].

4.16. General procedure for the hydrogenation of 10f and 10h to give 10b

A solution of the acetate (20 mg) in ethanol (2 mL) was treated with the appropriate catalyst (5% Pd/$CaCO_3$ for **10f**, 10% Pd/C for **10h**: 10 mg) and then hydrogenated until complete (1–2 h). The catalyst was filtered and the solvent removed under reduced pressure. Crude product was purified by preparative TLC, using PE–Et_2O 4:6 as eluent. The yield of this reaction was variable, due to the competitive hydrogenolysis to give 3-propylisoquinoline.

4.17. (±)-3-{1-[(*tert*-Butyldimethylsilyl)oxyethyl]}-isoquinoline 11a

4.17.1. Using TBDMS–Cl. A solution of **9a** (316 mg, 1.82 mmol) in dry DMF (6 mL) was treated with imidazole (317 mg, 4.66 mmol) and *tert*-butyldimethylsilyl chloride (537 mg, 3.55 mmol) and stirred at rt for 20 h. Since the reaction was not complete, further imidazole (37 mg, 543 μmol) and TBDMS–Cl (82 mg, 541 μmol) were added and the solution was stirred at 45°C for a further 2.5 h. The crude mixture was diluted with saturated aqueous $NaHCO_3$ and extracted with Et_2O. The organic extracts were then washed with water and brine. Chromatography with PE–Et_2O 8:2 gave pure **11a** as a pale yellow oil (462 mg, 88%).

4.17.2. Using TBDMS–OTf. A solution of **9a** (314 mg, 1.81 mmol) in dry CH_2Cl_2 (15 mL) was treated at 0°C with 2,6-lutidine (628 μL, 4.54 mmol) and *tert*-butyldimethylsilyl trifluoromethanesulfonate (833 μL, 3.62 mmol). After 20 min, since the reaction was com-

plete, work-up and chromatography were performed as described above to give **11a** (458 mg, 88%). R_f 0.39 (PE–Et_2O 8:2, **A**). IR: ν_{max} 2953, 2930, 1630, 1131, 1102, 827. GC–MS: R_t 7.78; m/z 287 (M^+, 0.07); 232 (5.0); 231 (20); 230 (100); 215 (6.6); 156 (28); 128 (13); 107 (6.4); 75 (25); 73 (10); 57 (5.5); 47 (6.2); 45 (6.1); 41 (7.2). ^{1}H NMR: 0.07 and 0.12 [6H, 2 s, Si(CH_3)$_2$]; 0.97 [9H, s, -C(CH_3)$_3$]; 1.55 [3H, d, CHCH_3, J=6.4]; 5.14 [1H, q, CHOTBDMS, J=6.4]; 7.55 [1H, ddd, H_7, J=8.0, 6.8, 1.2]; 7.67 [1H, ddd, H_6, J=8.1, 6.9, 1.3]; 7.83 [1H, d, H_5, J=7.0]; 7.85 [1H, s, H_4]; 7.95 [1H, d, H_8, J=8.0]; 9.17 [1H, s, H_1]. ^{13}C NMR: –4.87 and –4.77 [2C, Si(CH$_3$)$_2$]; 18.35 [-C(CH$_3$)$_3$]; 25.61 [CHCH$_3$]; 25.94 [3C, -C(CH$_3$)$_3$]; 71.92 [CHOTBDMS]; 115.01 [C_4]; 126.57 and 126.79 [2C, C_5, C_7]; 127.47 [C_8]; 127.62 [C_{8a}]; 130.20 [C_6]; 136.58 [C_{4a}]; 151.44 [C_1]; 159.42 [C_3].

4.18. (±)-3-{1-[(*tert*-Butyldiphenylsilyl)oxyethyl]}-isoquinoline 11b

The same procedure reported for the preparation of **11a** (with TBDMS–Cl) was followed, using *tert*-butyldiphenylsilyl chloride. The reaction was performed at 70°C and required further addition of imidazole (0.85 molar equivalents) and TBDPS–Cl (0.65 molar equivalents) after 21 h and warming again at 70°C for 72 h. Although the reaction was not complete, the work-up described above was followed. However, since TBDPS–Cl and TBDPS–OH could not be separated from **11b** after chromatography with PE–AcOEt 95:5→3:7 over silica gel, a second chromatographic separation over alumina (activity III) with PE–Et_2O 95:5→8:1 was performed. Compound **11b** was finally obtained as a pale yellow oil in 56% yield (71% on unrecovered starting material). R_f 0.32 (on silica gel, PE–Et_2O 8:2, **A**); 0.58 (on alumina, PE–Et_2O 8:2, **A**). IR: ν_{max} 2959, 2930, 1630, 1131, 1106. GC–MS: R_t 11.78 (usual analysis conditions were used but with final temp. 290°C for 4 min); m/z 411 (M^+, 0.03); 356 (8.1); 355 (31); 354 (100); 199 (17); 156 (9.6); 128 (5.4); 77 (7.1). ^{1}H NMR: 1.14 [9H, s, -C(CH_3)$_3$]; 1.44 [3H, d, CHCH_3, J=6.3]; 5.16 [1H, q, CHOTBDPS, J=6.4]; 7.19–7.78 [12H, m, H of Ph, H_6, H_7]; 7.82 [1H, d, H_5, J=8.1]; 7.90 [1H, s, H_4]; 7.94 [1H, d, H_8, J=8.7]; 9.12 [1H, s, H_1]. ^{13}C NMR: 19.36 [-C(CH$_3$)$_3$]; 25.33 [CHCH$_3$]; 27.07 [3C, -C(CH$_3$)$_3$]; 72.79 [CHOTBDPS]; 115.41 [C_4]; 126.54 and 126.75 [2C, C_5, C_7]; 127.40 [C_{8a}]; 127.45 and 127.52 [5C, *C meta* of Ph, C_8]; 129.50 and 129.61 [2C, *C para* of Ph]; 130.12 [C_6]; 133.60 and 134.25 [2C, *C ipso* of Ph]; 135.72 and 135.83 [4C, *C ortho* of Ph]; 136.45 [C_{4a}]; 151.39 [C_1]; 158.83 [C_3].

4.19. (±)-3-(1-Trityloxyethyl)isoquinoline 11c

A solution of **9a** (328 mg, 1.89 mmol) in dry 1,2-dichloroethane (15 mL)/pyridine (2 mL) was treated at 0°C with triphenylmethyl chloride (628 mg, 2.25 mmol). After 5 min the solution was heated to 60°C and stirred at this temperature for 3 days, while Ph_3CCl (157 mg) was added after the first 24 h. The mixture was diluted with water and extracted with AcOEt, after saturation of the aqueous phase with NaCl. Chromatography with PE–AcOEt 98:2→1:9 gave **11c** as a white foam (172 mg, 22%), with unreacted **9a** (220 mg, 66%). R_f 0.34 (PE–AcOEt 9:1, **A**, **B**). IR: ν_{max} 2977, 1630, 1074, 1031, 1002, 952, 890. GC–MS: R_t 12.75 (usual analysis conditions were used but with final temp. 290°C for 8 min); m/z 370 (M^+–45, 0.48); 244 (12); 243 (51); 239 (5.4); 234 (18); 233 (100); 232 (65); 228 (6.6); 166 (8.5); 165 (50); 157 (6.1); 156 (49); 129 (7.0); 128 (17); 105 (26); 77 (19). ^{1}H NMR: 1.31 [3H, d, CHCH_3, J=6.4]; 5.00 [1H, q, CHOTr, J=6.4]; 7.02–7.68 [19H, m, H of Ph, H_4, H_5, H_6, H_7]; 7.84 [1H, d, H_8, J=7.4]; 8.95 [1H, s, H_1]. ^{13}C NMR: 24.46 [CHCH$_3$]; 73.87 [CHOTr]; 87.92 [OCPh$_3$]; 116.17 [C_4]; 126.27 and 126.48 [2C, C_5, C_7]; 126.81 [3C, *C para* of Ph]; 127.04 [C_{8a}]; 127.28 [C_8]; 127.59 [6C, *C ortho* of Ph]; 128.98 [6C, *C meta* of Ph]; 129.91 [C_6]; 136.16 [C_{4a}]; 144.69 [3C, *C ipso* of Ph]; 150.90 [C_1]; 158.42 [C_3].

4.20. General procedure for the preparation of 12a–12c and 13a–13c from 11a–11c

A solution of compound **11** (300 μmol) in dry THF (8 mL) was treated, at –10°C, with solution of TMS-C≡CMgBr (0.5 M, 1.8 mL, 900 μmol), prepared as described in Section 4.6, and phenyl chloroformate (95 μl, 900 μmol). After 16–20 h the reaction was usually complete and was quenched with aqueous saturated NH_4Cl solution. After extraction with Et_2O, crude product was purified by chromatography with the appropriate PE–Et_2O mixtures.

4.20.1. 3-{(*S)-1-[(*tert*-Butyldimethylsilyl)oxyethyl]}-1-[(*S** or *R**)-(trimethylsilylethynyl)]-1*H*-isoquinoline-2-carboxylic acid phenyl esters 12a and 13a**. The mixture of **12a** and **13a** was isolated in 88% yield as a colourless oil. D.r. 87.3:12.7 was determined by gas chromatography (inj. temp. 220°C, det. temp. 220°C, oven temp. 230°C, carrier pressure (He) 1.2 kg/cm^2, flow 2.5 mL/min, split ratio≅50:1); R_t 18.83 (major diast.), 21.08 (minor diast.). R_f 0.58 (PE–Et_2O 95:5, **A**, **B**, both diast.). IR: ν_{max} 2954, 2175, 1722, 1323, 1182, 1134, 832. GC–MS (usual analysis conditions were used but with final temp. 290°C for 12 min); R_t 11.51 (major); m/z 490 (M^+–15, 2.9); 450 (14); 449 (38); 448 (100); 327 (9.6); 326 (5.6); 156 (8.9); 151 (24); 75 (6.5); 73 (34); 11.68 (minor); m/z 448 (M^+–57, 33); 327 (9.9); 326 (5.5); 252 (6.2); 157 (7.6); 156 (54); 151 (53); 100 (8.7); 77 (18); 75 (21); 74 (7.1); 73 (100); 45 (6.2); 44 (9.5); 43 (6.1); 40 (72). ^{1}H NMR (if not otherwise specified, signals are related to both diastereomers): 0.09 [9H, s, -Si(CH_3)$_3$]; 0.12 and 0.09 [6H, 2 s, Si(CH_3)$_2$]; 0.96 [9H, s, -C(CH_3)$_3$]; 1.45 [3H, d, CHCH_3, J=6.6]; 5.03 [1H, broad q, CHOTBDMS of minor, J=6.2]; 5.33 [1H, broad s, CHOTBDMS of major]; 6.34 [1H, s, H_1]; 6.76 [1H, d, H_4, J=1.3]; 7.09–7.46 [9H, m, aromatics]. ^{13}C NMR (major diast.): –4.96 and –4.80 [2C, Si(CH$_3$)$_2$]; –0.28 [3C, -Si(CH$_3$)$_3$]; 18.33 [-C(CH$_3$)$_3$]; 23.68 [CHCH$_3$]; 25.93 [3C, -C(CH$_3$)$_3$]; 49.77 [C_1]; 66.80 [CHOTBDMS]; 88.99 [-C≡C-TMS]; 102.02 [-C≡C-TMS]; 113.32 [C_4]; 121.57 [2C, *C ortho* of -OPh]; 125.31 [*C para* of -OPh]; 125.88, 125.98, 127.37 and 128.49 [4C, C_5, C_6, C_7, C_8]; 129.46 [2C, *C meta* of -OPh]; 130.51 [2C, C_3, C_{4a}]; 142.45 [C_{8a}]; 150.64 [2C, CO and *C ipso* of -OPh].

4.20.2. 3-{(*S)-1-[(*tert*-Butyldiphenylsilyl)oxyethyl]}-1-[(*S** or *R**)-(trimethylsilylethynyl)]-1*H*-isoquinoline-2-carboxylic acid phenyl esters 12b and 13b**. The mixture of **12b** and **13b** was isolated in 82% yield as a white foam. D.r. 94.6:5.4 was determined by ^{1}H NMR. R_f 0.39 (PE–Et_2O 95:5, **A**, **B**, both diast.). IR: ν_{max} 2961, 2171, 1719, 1329, 1132, 1112, 843. GC–MS: **12b** and **13b** were not suitable for this analysis. ^{1}H NMR (if not otherwise specified, signals are related to both diastereomers; spectrum in DMSO-d_6 at 100°C): 0.10 [9H, s, -Si(CH_3)$_3$]; 1.14 [9H, s, -C(CH_3)$_3$]; 1.34 [3H, d, CHCH_3, J=6.3]; 5.16 [1H, broad q, C*H*OTBDPS of minor, J=6.3]; 5.45 [1H, broad q, C*H*OTBDMS of major, J=6.1]; 6.90–7.69 [20H, m, H_1, H_4, aromatics]. ^{13}C NMR (major diast.): 0.28 [3C, -Si(*C*H$_3$)$_3$]; 19.48 [-*C*(CH$_3$)$_3$]; 23.54 [CH*C*H$_3$]; 27.12 [3C, -C(*C*H$_3$)$_3$]; 49.62 [C_1]; 67.80 [*C*HOTBDPS]; 89.03 [-C≡*C*-TMS]; 102.07 [-*C*≡C-TMS]; 113.71 [C_4]; 121.37 [2C, *C ortho* of -OPh]; 125.37 [*C para* of -OPh]; 125.64, 126.05, 127.53 and 128.35 [4C, C_5, C_6, C_7, C_8]; 127.53 [4C, *C meta* of Ph (TBDPS)]; 129.20 [2C, *C meta* of -OPh]; 129.58 and 129.63 [2C, *C para* of Ph (TBDPS)]; 130.52 and 132.02 [2C, C_3, C_{4a}]; 133.46 and 134.17 [2C, *C ipso* of Ph (TBDPS)]; 135.77 and 135.84 [4C, *C ortho* of Ph (TBDPS)]; 142.06 [C_{8a}]; 150.48 [2C, *C*O and *C ipso* of -OPh].

4.20.3. 1-[(*S or *R**)-(Trimethylsilylethynyl)]-3-{(*S**)-1-[trityloxyethyl]}-1*H*-isoquinoline-2-carboxylic acid phenyl esters 12c and 13c**. The mixture of **12c** and **13c** was isolated in 30% yield as a white foam. D.r. 90.4:9.6 was determined by ^{1}H NMR. R_f 0.34 (PE–Et_2O 95:5, **A**, **B**, both diast.). IR: ν_{max} 2957, 2170, 1722, 1189, 1083, 1013, 846. GC–MS: **12c** and **13c** were not suitable for this analysis. ^{1}H NMR (if not otherwise specified, signals are related to both diastereomers): 0.07 [9H, s, -Si(CH_3)$_3$]; 1.08 [3H, broad d, CHCH_3, J=5.7]; 4.97 [1H, q, C*H*OTr of minor, J=6.1]; 5.33 [1H, broad s, C*H*OTr of major]; 6.27 [1H, s, H_1]; 6.82–7.64 [25H, m, H_4, aromatics]. ^{13}C NMR (major diast.): –0.30 [3C, -Si(*C*H$_3$)$_3$]; 21.71 [CH*C*H$_3$]; 49.56 [C_1]; 68.30 [*C*HOTr]; 88.24 [-*C*Ph$_3$]; 89.08 [-C≡*C*-TMS]; 102.05 [-*C*≡C-TMS]; 113.00 [C_4]; 120.91 [2C, *C ortho* of -OPh]; 125.23 [*C para* of -OPh]; 125.98, 126.31, 127.80 and 128.25 [4C, C_5, C_6, C_7, C_8]; 127.03 [3C, *C para* of Ph (Tr)]; 127.68 [6C, *C ortho* of Ph (Tr)]; 129.10 [6C, *C meta* of Ph (Tr)]; 129.25 [2C, *C meta* of -OPh]; 129.46 and 130.49 [2C, C_3, C_{4a}]; 141.03 [C_{8a}]; 144.69 [3C, *C* ipso of Ph (Tr)]; 150.48 and 150.99 [2C, *C*O and *C ipso* of -OPh].

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