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# Studies of the formation of all-carbon quaternary centres, en route to lyngbyatoxin A. A comparison of phenyl and 7-substituted indole systems

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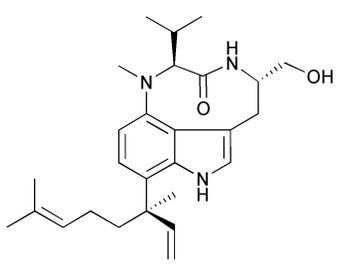
Copper mediated allylic substitutions and conjugate additions to geranyl, cinnamyl and allylic indole compounds have been investigated with the aim of finding a method for the creation of the all-carbon quaternary centre present in the natural product lyngbyatoxin A. Reaction conditions have been found giving a 68% $S_N2'$ selectivity in the copper mediated addition of PhMgBr to geranyl chloride, as well as 99% and 95% $S_N2'$ selectivity in the copper catalysed addition of EtMgBr to cinnamyl chloride and acetate, respectively. When the optimised reaction conditions were applied to the corresponding allylic compounds containing a 7-substituted indole moiety, the regioselectivity was reversed giving only the $S_N2$ product. The allylic indole-containing substrates were also found to be unproductive in Pd- or Mo-catalysed $S_N2'$-type substitution reactions. In related studies, copper catalysed conjugate addition of EtMgBr to the tricyclic lactam 6-methyl-pyrrolo[3,2,1-*ij*]quinolin-4-one gave a maximum of 20% of the 1,4-addition product.

## Introduction

In our ongoing efforts towards the stereoselective total synthesis of lyngbyatoxin A (Fig. 1), we have so far focused on the formation of the all-carbon quaternary centre.[1–3]




**Lyngbyatoxin A**

**Fig. 1**

We have previously succeeded in this by a Lewis acid mediated rearrangement of an appropriately substituted vinyl epoxide.[4] Having experienced a loss of enantiopurity and the outcome not being completely suitable for gram scale synthesis, we have however turned our attention towards allylic substitution ($S_N2'$) and conjugate addition reactions.

In our initial overall strategy we wished to prepare the trisubstituted indole **1**, in which the quaternary stereocentre is set and the indolactam ring could be formed subsequently (Scheme 1).

Strategy **A** is the most appealing approach for obtaining **1** since it involves a retrosynthetic disconnection between the indole and a geranyl species **2**, and the desired C–C bond formation could thus in principle be achieved *via* allylic substitution using an indolylcopper reagent.

It is however known[5–7] that the selectivity for such $S_N2'$ attack is poor for simple arylcopper reagents, so an alternative would be strategy **B** involving attack of an alkylcopper species on a substituted indole (**3**). Strategy **B** could also involve allylic substitution catalysed by palladium[8] or molybdenum[9–11] while strategies **C** and **D** are based on conjugate addition of an alkylcopper reagent to an indolyl-α,β-unsaturated ester (**4**) or tricyclic unsaturated lactam **5**.[12] All of these strategies would rely on the use of external chiral ligands to control absolute stereochemistry, but we decided to start our investigations in the racemic series. Furthermore, since relatively few methods have been developed for creation of all-carbon quaternary centres in which one of the substituents is an aromatic ring,[5,13–16] we decided to include the phenyl analogues in our exploratory studies of strategies **A** and **B**.

**Table 1** Testing CuCl·2LiCl[a]

| Entry | CuCl·2LiCl (equiv.) | Addition time (h) | $S_N2'$ | $S_N2$ |
|---|---|---|---|---|
| 1 | 0.1 | 2 | 22 | 78 |
| 2 | 0.2 | 2 | 40 | 60 |
| 3 | 1.05 | 2 | 40 | 60 |
| 4 | 1.05 | 10.5 | 42 | 58 |

[a] Reaction conditions: THF, 0 °C, Addition of geranyl chloride. Products were identified by $^1$H NMR.

## Results and discussion

### 1 Allylic substitution with an arylcopper reagent

Since the most convergent strategy is based on the connection of an indole and the alkyl side chain, we started our program with a study of allylic substitution by arylcopper species generated *in situ* from Grignard reagents, a reaction which has been investigated previously by Bäckvall *et al.*[5] (for Ar = phenyl in Scheme 2).

We started by repeating the work of Bäckvall *et al.*, using the CuCl·2LiCl system, and obtained a 22% yield of the $S_N2'$ product **6** (Table 1, entry 1), which corresponds well with the 18% reported.[5] Increasing the amount of copper to 0.2 equivalents led to the expected increase in **6** (40%) (Table 1, entry 2). However, neither increasing the amount of copper further to 1.05 equivalents nor increasing the addition time resulted in a better $S_N2'$ selectivity (Table 1, entries 3, 4).

As the CuCl·2LiCl system did not seem promising, we tested a range of different copper salts using the technique of "reverse addition", in which geranyl chloride is added to the reaction

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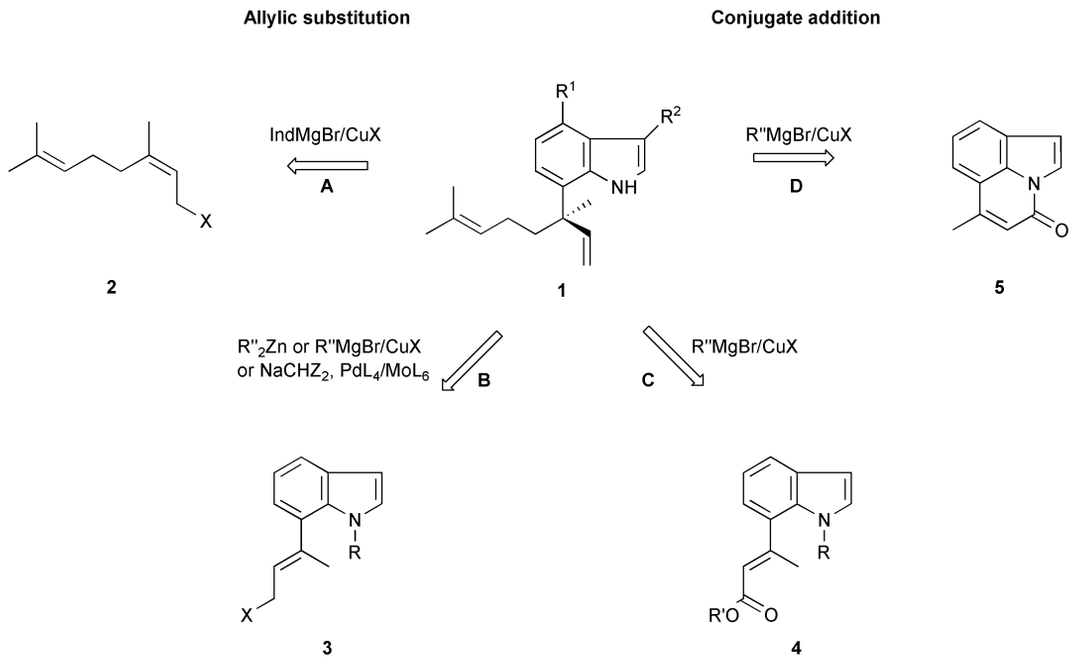
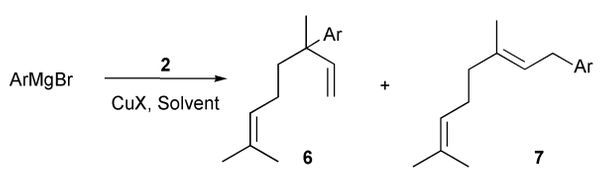



**Scheme 1** Strategies for creation of the quaternary centre.




**Scheme 2** Allylic substitution with an aryl copper reagent to give the $S_N2'$ product **6** or the $S_N2$ product **7**.

mixture containing the arylcopper magnesium reagent (Scheme 2). We observed that $S_N2'$-selectivity increased in the following order; CuCl < CuOTf < CuBr < CuI ≤ CuCN and that preformation of a stoichiometric arylcopper species is necessary for a high $S_N2'$ selectivity, since 0.2 equivalents of CuCN gave rise to only 9% of the $S_N2'$ product (**6**). In addition, if no copper salt was added only the $S_N2$ product (**7**) was observed. In the following we have focused on the regioselectivity of the reactions, but the isolated yields were consistently higher than 80%.

Examination of the leaving group on the geranyl species revealed that Cl > Br > OAc (Table 2), and in accordance with the observations published by Bäckvall's group it was found the addition of geranyl chloride over a shorter period (3.5 h *vs.* 10.5 h) gave a lower selectivity.

Interesting solvent effects were also observed (Table 3): dichloromethane and THF were equally good, but the results obtained in THF were very temperature-dependent, with an optimum around 20 °C, whereas selectivities in dichloromethane were consistently high (67–68%) at temperatures ranging from −50 to 20 °C.

By variation of the described reaction conditions an optimum of 68% $S_N2'$ selectivity was found using phenylmagnesium bromide, 1.05 eq. CuCN, 10.5 h addition time of geranyl chloride, 20 °C, and THF or dichloromethane as solvent. To our knowledge this is the best $S_N2'$ selectivity ever obtained for this substrate in a reaction involving arylcopper nucleophiles derived from Grignard reagents.[17]

Unfortunately, subjecting the Grignard reagent formed from *N*-allyl[18] (**8**) or *N*-tosyl[4] (**9**) protected 7-bromoindole to the optimised conditions gave mostly the reduced indole resulting from simple protonation of the indolylcopper or indolylmagnesium bromide reagent, and only traces of the substitution product could be identified by GC-MS.

**Table 2** Effect of leaving group[a]

| Entry | Leaving group | $S_N2'$ | $S_N2$ |
|---|---|---|---|
| 1 | Cl | 67 | 33 |
| 2 | Br | 59 | 41 |
| 3 | OAc | 0 | 100 |

[a] Reaction conditions: 1.05 eq. CuCN, THF, 25 °C, 10.5 h addition of geranyl compound. Products were identified by $^1$H NMR.

**Table 3** Effect of temperature[a]

| Entry | Temperature (°C) | Solvent | $S_N2'$ | $S_N2$ |
|---|---|---|---|---|
| 1 | −30 | THF | 12 | 88 |
| 2 | 20 | THF | 68 | 32 |
| 3 | 40 | THF | 66 | 34 |
| 4 | −50 | $CH_2Cl_2$ | 67 | 33 |
| 5 | 0 | $CH_2Cl_2$ | 68 | 32 |
| 6 | 20 | $CH_2Cl_2$ | 63 | 37 |

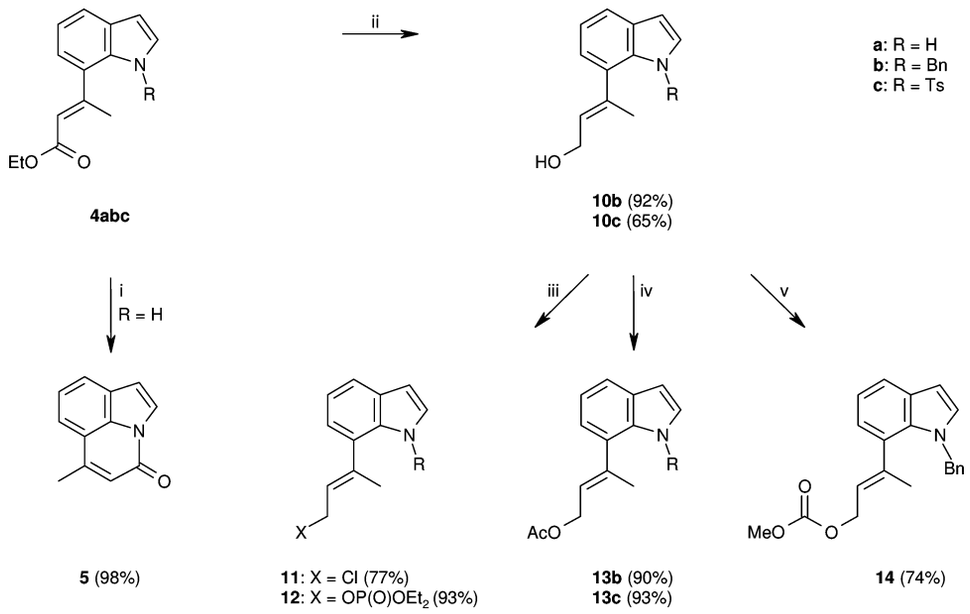
[a] Reaction conditions: 1.05 eq. CuCN, 10.5 h addition of geranyl chloride. The Grignard reagents were formed in THF. Products were identified by $^1$H NMR.

## 2 Allylic substitution with an alkylcopper reagent

Since the indolylcopper species were not useful nucleophiles in the allylic substitution, we then opted to incorporate the indole moiety in the allylic electrophile, and from our previous work[4] we knew that Heck reactions in the 7-position of the indole gave easy access to the required unsaturated system.

Starting from unprotected and *N*-benzyl protected 7-bromoindole, **4a** and **4b** were prepared by a modified literature procedure (Scheme 3).[4] The *trans* nature of the double bond was established by NOE experiments with the allylic alcohols (**10a**, **10b** and **10c**) showing NOE-effects between the methyl and the methylene group on the double bond.

The tosyl protected compound (**4c**) was more difficult to obtain, as the Heck reaction with *N*-tosylated 7-bromoindole gave a mixture of isomers, which could neither be separated as the α,β-unsaturated ester (**4c**), the allylic alcohol (**10c**) nor as the allylic acetate (**13c**). We, therefore, attempted to prepare **4c** by tosylation of **4a**, (NaH, TsCl) but the desired product was formed in only low yields (<20%), and the major product was



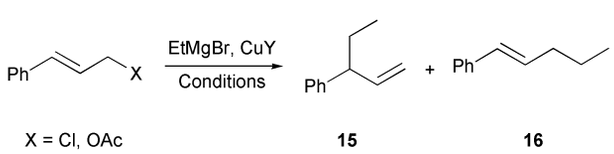

**Scheme 3** Synthesis of indole substrates. **a**: R = H, **b**: R = Bn, **c**: R = Ts. i) NaH, 0 ⟶ 20 °C. ii) Dibal-H, toluene, −50 ⟶ 20 °C. iii) $(EtO)_2POCl$, pyridine 0 ⟶ 20 °C. iv) $Ac_2O$, pyridine, 20 °C. v) $ClCO_2Me$, pyridine, 0 ⟶ 20 °C.

tricycle **5** (Scheme 3). In fact, **5** could be formed in quantitative yields by treatment of **4a** with NaH alone, giving an overall yield of 59% from 7-bromoindole compared to a literature report of a 12% yield from indoline.[12] Since this α,β-unsaturated lactam could be an interesting starting point for conjugate addition, it was included in the studies. By a selective reduction with Dibal-H the allylic alcohols (**10b** and **10c**) were prepared in good yield. From this point a range of different leaving groups could be introduced. In order to prepare the phosphate of the benzyl protected indole, **10b** was treated with diethyl chlorophosphate. However, only the corresponding chloride (**11b**), arising by chloride substitution of the initially formed phosphate group was isolated. Subjecting **10c** with the electron withdrawing tosyl protecting group to the same conditions afforded the desired phosphate (**12c**) along with 3% of the chloride.

The acetates **13bc** and the methyl carbonate **14** were prepared by standard procedures by treatment with acetic anhydride or methyl chloroformate and pyridine.

Aware of the structural similarity between the quaternary centre in the natural product sporochnol (synthesised recently by Hoveyda *et al.*[14]) and lyngbyatoxin A, we initiated model studies and were able to reproduce the excellent regioselectivity reported in the copper catalysed addition of diethylzinc to diethyl cinnamyl phosphate.[14] To our surprise, however, the indole system (in **12c** and **13bc**) once again proved to be recalcitrant and no reaction occurred either with or without the addition of CuCN.

We then turned to the copper catalysed reactions with alkyl Grignards; for the initial investigation and optimisation of reaction conditions we used the commercially available cinnamyl chloride and cinnamyl acetate together with ethylmagnesium bromide (Scheme 4).



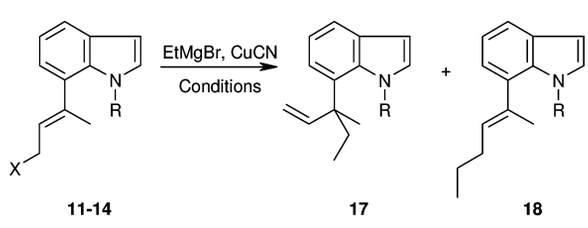

**Scheme 4** Allylic substitution with an alkylcopper reagent (Tables 4 and 5).

By variation of temperature and solvent, we found that the best conditions for copper catalysed allylic substitution using cinnamyl chloride were to perform the reactions in dichloromethane at low temperatures (Table 4, entries 3, 4, 7, and 8), which corresponds well with previous findings.[13] THF also gives selectivities above 90% at low temperatures (Table 4, entries 16 and 17) and this is convenient for cases in which dichloromethane is incompatible with the Grignard reagent. The solvent used for formation of the Grignard reagent (THF or diethyl ether) did not significantly influence the results.

In the study conducted by Alexakis *et al.*,[13] it was found that cinnamyl acetate favoured the $S_N2$ product under the conditions applied (−80 °C, $CH_2Cl_2$, triethyl phosphite). However, since the indole acetates were easily prepared we wanted to find reaction conditions favouring the $S_N2'$-product when an acetate was used as a leaving group. To our satisfaction, a high $S_N2'$-selectivity was achieved when the reactions were performed at higher temperatures (Table 5, entries 1, 5, 7, 10, and 11). Again the best solvent was dichloromethane, although this time the solvent for the Grignard reagent was very important, with diethyl ether providing significantly higher selectivities than THF. This is in line with a previous study by Bäckvall *et al.*[17] who used substrates which did not contain the cinnamyl moiety.

In order to test whether or not an extended addition time (5 h) would raise the selectivity, two experiments were performed under the optimum conditions determined; no significant change in selectivity was observed (Table 4, entry 9 and Table 5, entry 6).

Testing the conditions on the indole system showed yet again an unexpected lack of reactivity, as only **11b** and **12c** afforded products arising from substitution (Table 6, Scheme 5). In both cases the $S_N2$ product (**18**) was predominant and only traces of $S_N2'$-product (**17**) could be detected.




**Scheme 5** Allylic substitution with indole electrophiles.

In order to test if this reversal of selectivity in the indole systems was caused by increased steric hindrance, we synthesised the corresponding phenyl-analogue β-methylcinnamyl

**Table 4** Reaction between EtMgBr and cinnamyl chloride (Scheme 4)[a]

| Entry | Reaction solvent | Grignard solvent | Temperature (°C) | $S_N2'$ | $S_N2$ |
|---|---|---|---|---|---|
| 1 | $CH_2Cl_2$ | THF | 20 | 82 | 18 |
| 2 | $CH_2Cl_2$ | THF | 0 | 90 | 10 |
| 3 | $CH_2Cl_2$ | THF | −30 | 94 | 6 |
| 4 | $CH_2Cl_2$ | THF | −78 | 97 | 3 |
| 5 | $CH_2Cl_2$ | $Et_2O$ | 20 | 86 | 14 |
| 6 | $CH_2Cl_2$ | $Et_2O$ | 0 | 92 | 8 |
| 7 | $CH_2Cl_2$ | $Et_2O$ | −30 | 97 | 3 |
| 8 | $CH_2Cl_2$ | $Et_2O$ | −78 | 99 | 1 |
| 9[b] | $CH_2Cl_2$ | $Et_2O$ | −78 | 98 | 2 |
| 10[c] | $Et_2O$ | $Et_2O$ | 20 | 87 | 13 |
| 11 | $Et_2O$ | $Et_2O$ | 0 | 92 | 8 |
| 12 | $Et_2O$ | $Et_2O$ | −30 | 68 | 32 |
| 13 | $Et_2O$ | $Et_2O$ | −78 | 84 | 16 |
| 14 | THF | THF | 20 | 71 | 29 |
| 15 | THF | THF | 0 | 87 | 13 |
| 16 | THF | THF | −30 | 92 | 8 |
| 17 | THF | THF | −78 | 94 | 6 |

[a] Reaction conditions: 10% CuCN, 20% triethyl phosphite, 30 min addition time plus 10 min reaction. Products were identified by GC. [b] 5 h addition time. [c] Without addition of triethyl phosphite the relationship is 80 : 20.

**Table 5** Reaction between EtMgBr and cinnamyl acetate (Scheme 4)[a]

| Entry | Reaction solvent | Grignard solvent | Temperature (°C) | $S_N2'$ | $S_N2$ |
|---|---|---|---|---|---|
| 1 | $CH_2Cl_2$ | THF | 20 | 89 | 11 |
| 2 | $CH_2Cl_2$ | THF | 0 | 47 | 53 |
| 3 | $CH_2Cl_2$ | THF | −30 | 6 | 94 |
| 4 | $CH_2Cl_2$ | THF | −78 | 5 | 95 |
| 5 | $CH_2Cl_2$ | $Et_2O$ | 20 | 94 | 6 |
| 6[b] | $CH_2Cl_2$ | $Et_2O$ | 20 | 94 | 6 |
| 7 | $CH_2Cl_2$ | $Et_2O$ | 0 | 95 | 5 |
| 8 | $CH_2Cl_2$ | $Et_2O$ | −30 | 79 | 21 |
| 9 | $CH_2Cl_2$ | $Et_2O$ | −78 | 46 | 54 |
| 10 | $Et_2O$ | $Et_2O$ | 20 | 87 | 13 |
| 11 | $Et_2O$ | $Et_2O$ | 0 | 86 | 14 |
| 12 | $Et_2O$ | $Et_2O$ | −30 | 33 | 67 |
| 13 | $Et_2O$ | $Et_2O$ | −78 | 48 | 52 |
| 14 | THF | THF | 20 | 7 | 93 |
| 15 | THF | THF | 0 | 6 | 94 |
| 16 | THF | THF | −30 | 4 | 96 |
| 17 | THF | THF | −78 | 7 | 93 |

[a] Reaction conditions: 10% CuCN, 20% triethyl phosphite, 30 min addition time plus 10 min reaction. Products were identified by GC. [b] 5 h addition time.

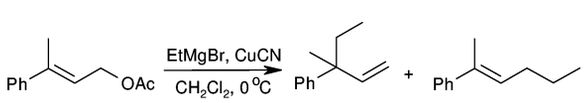
**Table 6** Allylic substitution with indole electrophiles[a]

| Compound | R | X | Reaction solvent | Temperature (°C) | $S_N2'$ | $S_N2$ |
|---|---|---|---|---|---|---|
| **11** | Bn | Cl | $Et_2O$ | 0 | <5 | >95 |
| **11** | Bn | Cl | $CH_2Cl_2$ | −78 | — | — |
| **12** | Ts | $OPO(EtO)_2$ | $CH_2Cl_2$ | 20 | <5 | 62[b] |
| **13b** | Bn | OAc | $Et_2O$ | 0 | — | — |
| **13b** | Bn | OAc | $CH_2Cl_2$ | 20 | — | — |
| **13c** | Ts | OAc | $CH_2Cl_2$ | 0 | —[c] | — |
| **14** | Bn | $OCO_2Me$ | $CH_2Cl_2$ | −78 ⟶ 20 | —[d] | — |

[a] EtMgBr (in ether), 50% CuCN, 100% triethyl phosphite, 30 min addition time plus 24 h reaction. Products were identified by $^1$H NMR. [b] 33% of the allylic alcohol **10c**. [c] Quantitative reaction with the acetate giving the allylic alcohol **10c** as the sole product. [d] Decomposition of starting material.

acetate (**19**) by Dibal-H reduction[19] of ethyl β-methylcinnamate followed by a standard acetylation (Scheme 6).

Performing the allylic substitution, employing the optimum conditions determined for cinnamyl acetate (Table 5, entry 7),

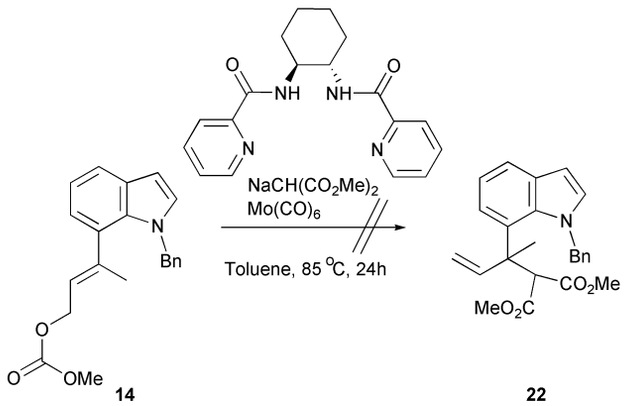



**19** **20** (90%) **21** (10%)

**Scheme 6** Allylic substitution with β-methylcinnamyl acetate.

we observed only a slight loss of $S_N2'$-selectivity (from 95% to 90%). The complete reversal of selectivity seen in the indole series is, therefore, not caused solely by the extra methyl group on the double bond as compared to cinnamyl acetate.

Having synthesised the allylic indole compounds we then tested the molybdenum catalysed allylic alkylation, which has proven to be very selective towards the branched product when cinnamyl methyl carbonate was used as electrophile.[9] We were able to reproduce the excellent selectivity reported for the cinnamyl system, but for the indole system in **14**, no reaction occurred (Scheme 7).




14 22

**Scheme 7** Molybdenum catalysed allylic alkylation.

The use of $Pd(PPh_3)_4$ as a precatalyst was equally unsuccessful, and only the more reactive complex $PdCl(allyl)PPh_3$[20] gave a trace of the substituted product. Molecular modeling[21,22] of the ($\eta^3$-allyl)palladium complex (Fig. 2) indicates that it is very strained and, indeed, unlikely to be formed. In addition, the modelling also shows that the *N*-benzyl protecting group efficiently blocks the approach of any external nucleophile to the face of the π-allyl system opposite the palladium.

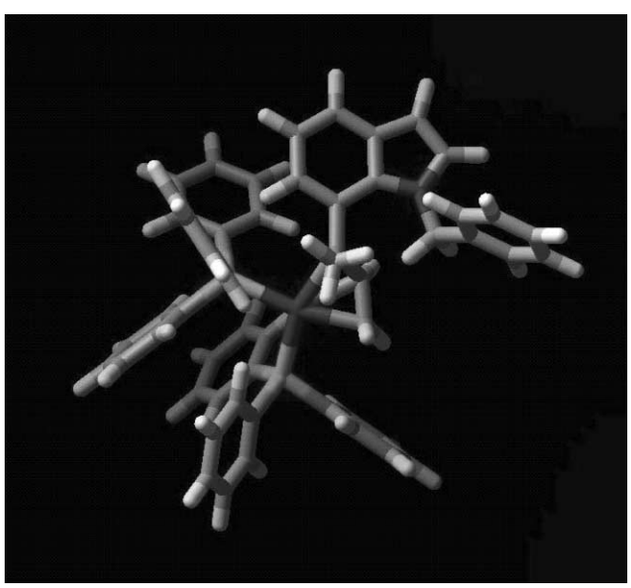


**Fig. 2** Low energy conformation of the ($\eta^3$-allyl)palladium complex with two $PPh_3$ ligands. Calculated using Macromodel 8.0.[21]

## 3 Conjugate addition

We then turned our attention to the copper catalysed conjugate addition of an alkyl Grignard reagent to the α,β-unsaturated esters **4bc** with ethylmagnesium bromide being chosen as a simple model (Scheme 8 and Table 7).

To our surprise, no reaction with the *N*-protected indoles occurred, not even 1,2-addition to give **24bc** and at present we have no convincing explanation for this lack of reactivity. We then tried to use the unprotected compound **4a** with an extra equivalent of Grignard reagent to deprotonate the indole nitrogen. Interestingly, we now obtained the 1,2-addition product **24a** but also 21% of a tricyclic product (**25**) with the desired quaternary centre. In this case it is possible that the alkyl group is delivered intramolecularly *via* a precoordination of the Grignard reagent to the indole nitrogen. It was not possible to suppress the formation of **24a** by increasing the amount of CuCN and, surprisingly, an experiment without CuCN gave the same product distribution as with CuCN (Table 7).

**Table 7** Conjugate addition to α,β-unsaturated esters (Scheme 8)[a]

| Compound | R | **23** : **24** : **25** | Yield (%) |
|---|---|---|---|
| **4a**[b] | H | 0 : 79 : 21 | 82 |
| **4a**[c] | H | 0 : 0 : 0 | — |
| **4a**[d] | H | 0 : 78 : 22 | 82 |
| **4b** | Bn | 0 : 0 : 0 | — |
| **4c** | Ts | 0 : 0 : 0 | — |

[a] Reaction conditions see Scheme 8. Products were identified by $^1H$ NMR. [b] 2.0 equivalents EtMgBr. [c] 2.0 equivalents EtMgBr and CuCN. [d] 2.0 equivalents EtMgBr and no CuCN.

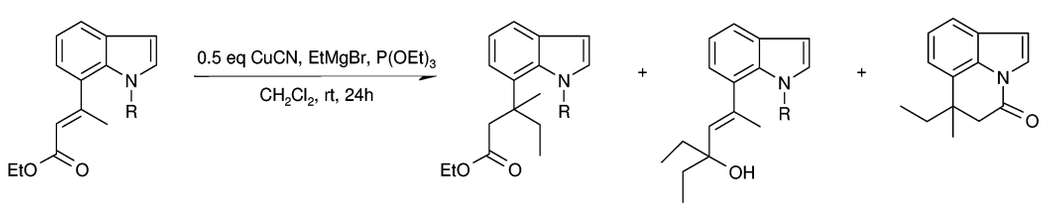
**Table 8** Conjugate addition to **5** (Scheme 10)[a]

| Entry | Solvent | Additives | Conversion (%) |
|---|---|---|---|
| 1 | $CH_2Cl_2$ | — | — |
| 2 | $CH_2Cl_2$ | $P(OEt)_3$[b] | 13 |
| 3 | $CH_2Cl_2$ | $P(OEt)_3$[b], TMSCl[c] | 19 |
| 4 | $CH_2Cl_2$ | $P(OEt)_3$[b], $BF_3(OEt)_2$[c] | — |
| 5 | $CH_2Cl_2$ | $P(OEt)_3$[b], DMPU[c] | 11 |
| 6 | $CH_2Cl_2$ | $P(OEt)_3$[b], HMPA[c] | — |
| 7[d] | $CH_2Cl_2$ | $P(OEt)_3$[b] | 7 |
| 8[e] | $CH_2Cl_2$ | P(OEt)3[b], TMSCl[c] | —[f] |
| 9 | $CH_2Cl_2$ | $P(OEt)_3$[b], TMSCl[c], HMPA[c] | 12 |
| 10 | THF | $P(OEt)_3$[b] | — |
| 11 | THF | $P(OEt)_3$[b], TMSCl[c] | — |
| 12 | THF | $P(OEt)_3$[b], TMSCl[c], HMPA[c] | — |
| 13 | $Et_2O$ | $P(OEt)_3$[b] | 17 |
| 14 | $Et_2O$ | $P(OEt)_3$[b], TMSCl[c] | 7 |
| 15 | $Et_2O$ | $P(OEt)_3$[b], HMPA[c] | 1 |
| 16 | $Et_2O$ | $P(OEt)_3$[b], TMSCl[c], HMPA[c] | 20 |

[a] Reaction conditions: 1 eq. EtMgBr (in ether), 0.5 eq. CuCN, rt, 24 h. Products were identified by GC. [b] 1 eq. [c] 2 eq. [d] EtMgBr (in THF) was used. [e] 1.5 eq. of EtMgBr (in ether). [f] Decomposition of starting material.

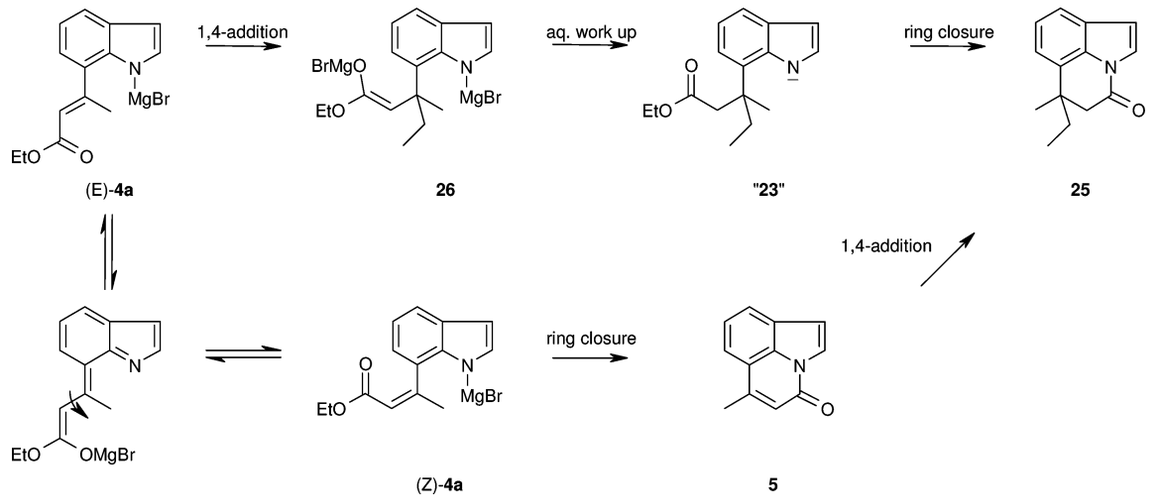
The tricyclic compound (**25**) could be formed by two pathways (Scheme 9). The first possibility is a 1,4-attack on the α,β-unsaturated ester (*E*)-**4a** followed by ring closure during aqueous work up. The second possibility is a *trans*/*cis* isomerisation after the initial deprotonation of the indole nitrogen. The *cis* isomer (*Z*)-**4a** is then ready for a ring closure followed by a 1,4-addition.

Encouraged by the formation of **25** we tried the conjugate addition to the tricycle using the same conditions as before (Scheme 10), and satisfyingly we again saw the formation of **25** (Table 8, entry 2). In an experiment without copper, no reaction was observed.

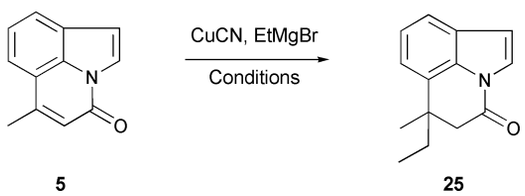



**4abc** **23abc** **24abc** **25**

**Scheme 8** Conjugate addition to α,β-unsaturated esters (Table 7).




**Scheme 9** Possible mechanism for the formation of **25**.




**Scheme 10** Conjugate addition to unsaturated lactam **5** (Table 8).

Despite the low yield, we felt the result was promising enough to warrant further investigation, as detailed in Table 8. To our disappointment, however, only low yields (0–20%) were obtained, the best conditions being diethyl ether or dichloromethane as solvent with addition of triethyl phosphite, TMSCl, and HMPA. Besides the conditions listed in Table 8, we also tried other copper sources (CuI, CuBr, $Cu(OTf)_2$) and another preformed cuprate ($Bu_2CuLi$) in combination with the additives referred to above. None of these experiments gave rise to any of the desired product.

## Conclusion

Although the experiments involving indole moieties (in either the nucleophilic or the electrophilic components of the reactions studied) were unsuccessful, our investigations involving the corresponding phenyl compounds have led to several new findings. Thus, the regioselectivity obtained in the allylic substitution of geranyl chloride with a an arylcopper reagent represents a significant improvement on earlier results[5] and, as far as we are aware, the 68 : 32 ratio in favour of the $S_N2'$ product is the best yet recorded for this substrate. Furthermore, synthetically useful reaction conditions for $S_N2'$ substitutions involving cinnamyl chloride (99% $S_N2'$) and cinnamyl acetate (95% $S_N2'$) have been identified. The results involving cinnamyl acetate are especially valuable, since this substrate has not previously been reported to favour $S_N2'$ substitution. The efficient formation of the tricyclic lactam **5** in two steps from 7-bromoindole is also noteworthy, and this type of reaction sequence should provide a rapid entry to tricyclic alkaloid systems *e.g.* hippadine.[23]

The large differences in reactivity between the phenyl and 7-substituted indole (for the range *N*-H, *N*-Bn or *N*-Ts) substrates were unexpected, and our results underline the limitations of some contemporary methods for the formation of all-carbon quaternary centres. Since the strategies outlined above for the formation of the desired quaternary centre in lyngbyatoxin A were unsuccessful, we are currently exploring routes based on allylic substitution using appropriately substituted aryl species which will allow formation of the indole moiety at a later stage in the synthesis.

## Experimental

Tetrahydrofuran and diethyl ether were distilled under nitrogen from sodium/benzophenone prior to use. Dichloromethane was distilled under nitrogen from calcium hydride prior to use. Methyl methacrylate, ethyl crotonate, and $Ti(O^iPr)_4$ were vacuum distilled before use. All other commercially available compounds were used as received. Dichlorobis(tri-*o*-tolylphosphine)palladium(II),[24] tetrakis(triphenylphosphine)palladium(0),[25] chloro(allyl)(triphenylphosphine)palladium(II),[20] (*S*,*S*)-*N*,*N*′-bis(2-pyridinecarboxamide)-1,2-cyclohexane,[26] *N*-allyl-7-bromoindole,[18] *N*-tosyl-7-bromoindole,[4] **4b**,[4] and **10b**[4] were synthesised following literature procedures. All air- and moisture-sensitive reactions were carried out under argon in oven-dried glassware. For prolonged addition times a syringe pump was used. It was not possible to obtain good microanalyses of the indole compounds due to their instability, so these were characterised by HRMS. $^1H$ (300 or 500 MHz) and $^{13}C$ (75 or 125 MHz) NMR spectra were recorded on a Varian Mercury 300 or a Varian Inova 500, respectively. IR spectra were recorded on a Perkin Elmer 1600 series FT-IR. High resolution mass spectra were provided by the Department of Chemistry, University of Copenhagen.

### General procedure for allylic substitutions with arylcopper reagents

Bromobenzene (60 µl, 0.57 mmol) was added over a period of 30 min (with a syringe pump) to a suspension of Mg (28 mg, 1.1 mmol) in THF (1 ml), and the reaction mixture was stirred vigorously at 20 °C for 30 min. The solution of phenylmagnesium bromide was then added over a period of 1 h (with a syringe pump) to a suspension of CuCN (51 mg, 0.57 mmol) in THF or dichloromethane (2 ml) at 0 °C. Then a solution of geranyl chloride (100 µl, 0.54 mmol) in THF or dichloromethane (1 ml) was added over 10.5 h at the chosen temperature. When the addition was complete, the mixture was stirred for another hour before quenching with a buffer solution ($NH_4Cl/NH_4OH$ (sat), pH = 8–9, 3 ml). The mixture was extracted with dichloromethane (3 × 10 ml), dried ($MgSO_4$), and evaporated to give ≈110–115 mg of a yellow oil. The products (**6** and **7**) could be isolated by column chromatography (pentane/diethyl ether 95 : 5). Spectral data were in accordance with those previously published.[5]

### General procedure for allylic substitutions with alkylcopper reagents

**Reaction with cinnamyl chloride.** To a suspension of CuCN (7 mg, 0.08 mmol) in solvent (5 ml) was added triethyl phosphite (0.03 ml, 0.17 mmol) and the mixture was stirred at

room temperature for 15 min until the CuCN was fully dissolved. The mixture was then cooled to the appropriate temperature and cinnamyl chloride was added (0.10 ml, 0.72 mmol). To the mixture was added EtMgBr (0.80 mmol) dropwise over 30 min, and the reaction mixture was stirred for an additional 10 min. The products were identified by $^1$H NMR and the distribution was analysed by GC. Spectral data were in accordance with those previously published (**15**[14] and **16**[27]).

**Reaction with cinnamyl acetate.** To a suspension of CuCN (5 mg, 0.06 mmol) in solvent (5 ml) was added triethyl phosphite (0.02 ml, 0.11 mmol) and the mixture was stirred at room temperature for 15 min until the CuCN was fully dissolved. The mixture was then cooled to the appropriate temperature and cinnamyl acetate was added (0.10 ml, 0.60 mmol). To the mixture was added EtMgBr (0.65 mmol) dropwise over 30 min, and the reaction mixture was stirred for an additional 10 min. The products were identified by $^1$H NMR and the distribution was analysed by GC. Spectral data were in accordance with those previously published (**15**[14] and **16**[27]).

**Reaction with allylic indoles 11–14.** To a suspension of CuCN (50 mol%) in diethyl ether or dichloromethane (5 ml) at room temperature was added diethyl phosphite (100 mol%). The reaction was allowed to stir for 15 min until all CuCN was dissolved. The mixture was then cooled to the appropriate temperature and the indole substrate (100 mol%) and EtMgBr (100 mol%) were added with an addition time of 30 min. The mixture was kept stirring for 24 hours and quenched with water (5 ml) and extracted with dichloromethane (3 × 5 ml), dried ($MgSO_4$) and evaporated. Product distribution was determined by crude $^1$H NMR on the crude product. The $S_N2'$ products could not be isolated due to the small amount formed.

**18b** $^1$H NMR ($CDCl_3$) $\delta$ 7.55 (d, $J$ = 7.8 Hz, 1H), 7.23 (m, 3H), 7.07 (t, $J$ = 7.3 Hz, 1H), 7.03 (d, $J$ = 3.2 Hz, 1H), 6.88 (dd, $J$ = 1.5, 7.2 Hz, 1H), 6.86 (d, $J$ = 6.1 Hz, 2H), 6.57 (d, $J$ = 3.2 Hz, 1H), 5.47 (br s, 2H), 5.36 (tq, $J$ = 1.5, 7.2 Hz, 1H), 2.08 (br s, 2H), 1.80 (s, 3H), 1.34 (m, 2H), 0.90 (t, $J$ = 7.3 Hz, 3H). $^{13}$C NMR ($CDCl_3$) $\delta$ 139.1, 133.7, 132.9, 130.6, 129.8, 128.4, 127.0, 126.1, 126.4, 124.3, 122.9, 120.3, 119.3, 102.3, 51.2, 30.4, 22.4, 19.2, 13.9. MS: *m*/*z* (EI) 289.1835 ($M^+$. $C_{21}H_{23}N$ requires 289.1830), 289, 198, 168, 91.

**18c** $^1$H NMR ($CDCl_3$) $\delta$ 7.64 (d, $J$ = 3.8 Hz, 1H), 7.42 (d, $J$ = 8.4 Hz, 2H), 7.35 (dd, $J$ = 1.4, 7.7 Hz, 1H), 7.15 (t, $J$ = 7.5 Hz, 1H), 7.09 (d, $J$ = 7.9 Hz, 2H), 7.03 (dd, $J$ = 1.4, 7.4 Hz, 1H), 6.67 (d, $J$ = 3.7 Hz, 1H), 5.21 (tq, $J$ = 1.3, 7.1 Hz, 1H), 2.31 (s, 3H), 2.12 (q, $J$ = 7.4 Hz, 2H), 2.02 (d, $J$ = 1.3 Hz, 3H), 1.48 (m, 2H). $^{13}$C NMR ($CDCl_3$) $\delta$ 148.1, 144.3, 137.0, 135.4, 135.2, 133.4, 130.8, 129.4, 129.1, 127.5, 126.9, 124.3, 119.9, 111.2, 30.6, 22.8, 21.7, 18.7, 14.3. MS: *m*/*z* (EI) 353.1454 ($M^+$. $C_{21}H_{23}NO_2S$ requires 353.1450).

### General procedure for the copper catalysed conjugate addition of EtMgBr to 4abc

To a suspension of CuCN (0–100 mol%) in dichloromethane (5 ml) at room temperature was added triethyl phosphite (0–100 mol%) and the mixture was allowed to stir for 15 min. until CuCN was fully dissolved. To this mixture was added the indole substrate **4abc** (100 mol%, ≈100 mg) and EtMgBr (100–200 mol%) dropwise over 10 min. The mixture was allowed to stir at room temperature for 24 hours and quenched with water (5 ml) and extracted with dichloromethane (3 × 5 ml). $^1$H NMR provided the product distribution.

**24a**: $^1$H NMR ($CDCl_3$) $\delta$ 8.33 (bs, 1H), 7.54 (d, $J$ = 7.4 Hz, 1H), 7.23 (t, $J$ = 2.7 Hz, 1H), 7.11 (d, $J$ = 7.3 Hz, 1H), 7.07 (dd, $J$ = 1.5, 7.3 Hz, 1H), 6.58 (dd, $J$ = 2.3, 3.2 Hz, 1H), 5.70 (d, $J$ = 1.2 Hz, 1H), 2.36 (d, $J$ = 1.2 Hz, 3H), 1.74 (q, $J$ = 7.5 Hz, 4H), 1.02 (t, $J$ = 7.5 Hz, 6H). $^{13}$C NMR ($CDCl_3$) $\delta$ 136.3, 134.1, 130.0, 128.3, 124.3, 124.7, 120.4, 120.0, 119.5, 103.2, 54.7, 34.4, 18.8, 8.6. IR (KBr, $\nu_{max}$/cm$^{-1}$): 3420, 2968, 2934, 1026, 946, 797, 730. MS: *m*/*z* (EI) 243.1620 ($M^+$. $C_{16}H_{21}NO$ requires 243.1623).

**25**: $^1$H NMR ($CDCl_3$) $\delta$ 7.67 (d, $J$ = 3.6 Hz, 1H), 7.47 (dd, $J$ = 1.0, 7.8 Hz, 1H), 7.26 (t, $J$ = 7.6 Hz, 1H), 7.17 (dd, $J$ = 0.9, 7.4 Hz, 1H), 6.71 (d, $J$ = 3.6 Hz, 1H), 2.90 (d, $J$ = 16.5 Hz, 1H), 2.81 (d, $J$ = 16.5 Hz, 1H), 1.75 (m, 2H), 1.43 (s, 3H), 0.81 (t, $J$ = 7.5 Hz, 3H). $^{13}$C NMR ($CDCl_3$) $\delta$ 158.5, 148.5, 132.0, 127.5, 124.9, 123.4, 123.0, 121.4, 121.1,118.0, 110.1, 17.4. IR (KBr, $\nu_{max}$/cm$^{-1}$): 2965, 1718, 1440, 1390, 1304, 801, 735. MS: *m*/*z* (EI) 213.1161 ($M^+$. $C_{14}H_{15}NO$ requires 213.1154), 213, 184, 154.

### General procedure for the copper catalysed conjugate addition of EtMgBr to 5

To a suspension of CuX (50 mol%) in solvent (THF, dichloromethane or $Et_2O$) (5 ml) at room temperature was added the appropriate additives and **5** (100 mol%, 50–100 mg). The reaction was stirred at room temperature for 15 min and EtMgBr was added dropwise over 10 min. The mixture was kept stirring for 24 h, whereafter it was quenched with water (5 ml), extracted with DCM (3 × 5 mL) and dried ($MgSO_4$). The solvent was evaporated and the extent of conversion was determined by $^1$H NMR on the crude product.

**25**: See above.

### Indole chemistry

***(E)*-Ethyl 3-(indol-7-yl)-crotonate (4a).** $PdCl_2(P(o\text{-tol})_3)_2$ (400 mg, 0.51 mmol), 7-bromoindole (2.00 g, 10.3 mmol), triethylamine (25 ml, 180 mmol) and tetrabutylammonium bromide (800 mg, 2.48 mmol) were added to a solution of ethyl crotonate (30 ml, 241 mmol) in DMF (100 ml) and stirred for 120 min at 90 °C. The mixture was cooled to room temperature, diluted with ethyl acetate (100 ml) and washed with brine (200 ml). The aqueous layer was extracted with diethyl ether (3 × 100 ml) and the combined organic phases were dried ($MgSO_4$) and evaporated to a dark liquid, which, in addition to product, contained traces of DMF. After three purification steps by column chromatography (ethyl acetate/hexane 1 : 10) 1.42 g (60%) of the desired product was obtained.

$^1$H NMR ($CDCl_3$) $\delta$ 8.47 (br s, 1H), 7.38 (d, $J$ = 7.7 Hz, 1H), 7.25 (t, $J$ = 2.7 Hz, 1H), 7.19 (dd, $J$ = 1.1, 7.3 Hz, 1H), 7.15 (t, $J$ = 7.6 Hz, 1H), 6.60 (dd, $J$ = 2.1, 3.2 Hz, 1H), 6.27 (q, $J$ = 1.3 Hz, 1H), 4.26 (q, $J$ = 7.2 Hz, 2H), 2.69 (s, 3H), 1.35 (t, $J$ = 7.2 Hz, 2H). $^{13}$C NMR ($CDCl_3$) $\delta$ 167.1, 155.2, 132.5, 128.7, 126.8, 124.8, 121.4, 120.6, 119.7, 118.1, 102.9, 60.1, 19.7, 14.3. IR (KBr, $\nu_{max}$/cm$^{-1}$): 3448, 1654, 1420. MS: *m*/*z* (EI) 229.1109 ($M^+$. $C_{14}H_{15}NO_2$ requires 229.1103), 229, 184, 154, 77.

***(E)*-Ethyl 3-(*N*-*p*-toluenesulfonylindol-7-yl)-crotonate (4c).** *p*-Toluenesulfonyl chloride (3.0 g, 15.7 mmol) was added to a 0 °C solution of **4a** (906 mg, 3.95 mmol) in THF (50 ml), and the mixture was stirred for 5 min. Then NaH (55% in mineral oil, 200 mg, 4.0 mmol) was added, and the greyish mixture was stirred for 30 h at 0 °C. Column chromatography (ethyl acetate/heptane 1 : 9) afforded 214 mg (14%) of the product as a red/brown oil. Recovered starting material (760 mg, 84%).

$^1$H NMR ($CDCl_3$) $\delta$ 7.64 (d, $J$ = 3.8 Hz, 1H), 7.45 (dd, $J$ = 1.3, 7.8 Hz, 1H), 7.42 (d, $J$ = 8.4 Hz, 2H), 7.20 (t, $J$ = 7.6 Hz, 1H), 7.13 (d, $J$ = 8.4 Hz, 1H), 7.06 (dd, $J$ = 1.3, 7.5 Hz, 1H), 6.71 (d, $J$ = 3.8 Hz, 1H), 5.64 (q, $J$ = 1.3 Hz, 1H), 4.22 (q, $J$ = 7.1 Hz, 2H), 2.58 (d, $J$ = 1.3 Hz, 3H), 2.32 (s, 3H). $^{13}$C NMR ($CDCl_3$) $\delta$ 166.7, 158.4, 144.7, 134.9, 133.6, 132.9, 132.1, 130.8, 129.6, 126.9, 126.1, 124.4, 121.5, 118.7, 111.4, 60.0, 21.8, 21.5, 14.6. IR (KBr, $\nu_{max}$/cm$^{-1}$): 3159, 2976, 1713, 1638, 1348, 1189, 1172, 1128, 1092, 801, 720, 680. MS: *m*/*z* (EI) 383.1173 ($M^+$. $C_{21}H_{21}NO_4S$ requires 383.1191), 383, 184, 154, 91.

**6-Methyl-pyrrolo[3,2,1-*ij*]quinolin-4-one (5).** NaH (55% in mineral oil, 300 mg, 12.5 mmol) was added to a solution of **4a** in THF (200 ml) at 0 °C. The ice bath was removed, and stirring

was continued for 2 h. Then the reaction was quenched with water (200 ml) and evaporated. Water (50 ml) and diethyl ether (50 ml) were added, and extraction with diethyl ether (5 × 50 ml), drying ($MgSO_4$) of the combined organic phases and evaporation gave 234 mg (98%) of the desired product as a light green solid.

$^1$H NMR ($CDCl_3$) $\delta$ 8.42 (d, $J$ = 3.7, 1H), 7.92 (d, $J$ = 3.5, 1H), 7.83 (d, $J$ = 7.6, 1H), 7.42 (t, $J$ = 7.6, 1H), 6.67 (d, $J$ = 7.6, 1H), 6.53 (d, $J$ = 1.2, 1H), 2.57 (d, $J$ = 1.2, 3H). $^{13}$C NMR ($CDCl_3$) $\delta$ 159.0, 149.0, 132.5, 127.5, 124.9, 123.4, 122.9, 121.4, 121.1, 110.1, 17.4. IR (KBr, $\nu_{max}$/cm$^{-1}$): 2923, 1664, 1626, 1599, 1448, 1316, 1118, 808. MS: *m*/*z* (EI) 183.0676 ($M^+$. $C_{12}H_9NO$ requires 183.0684), 183, 154, 127, 77. Mp: 142–143 °C.

**(*E*)-3-(*N*-*p*-Toluenesulfonylindol-7-yl)-)-but-2-en-1-ol (10c).** Dibal-H (1.2 M in toluene, 6.0 ml, 7.2 mmol) was added dropwise to a −78 °C solution of **4c** in toluene (60 ml), and the reaction mixture was stirred for 3 h during which the temperature gradually reached 20 °C. The mixture was diluted with dichloromethane (100 ml) and Rochelle's salt (sat. 100 ml) was added. The aqueous layer was extracted with dichloromethane (3 × 100 ml) and the combined organic phases were dried ($MgSO_4$) and evaporated. Column chromatography (ethyl acetate/hexane 1 : 1) afforded 444 mg (65%) of the desired product as colourless crystals.

$^1$H NMR ($CDCl_3$) $\delta$ 7.60 (d, $J$ = 3.5, 1H), 7.44 (d, $J$ = 8.0, 2H), 7.38 (d, $J$ = 7.7, 1H), 7.18 (t, $J$ = 6.8, 1H), 7.13 (d, $J$ = 8.0, 2H), 7.07 (d, $J$ = 7.4, 1H), 6.68 (d, $J$ = 3.8, 1H), 5.63 (t, $J$ = 8.1, 1H), 4.33 (br s, 1H), 2.31 (s, 3H), 2.12 (s, 3H). $^{13}$C NMR ($CDCl_3$) $\delta$ 144.4, 140.6, 134.5, 133.8, 133.3, 132.7, 130.7, 129.3, 126.8, 126.6, 126.5, 124.3, 120.3, 111.6, 59.2, 21.4, 18.4. IR (KBr, $\nu_{max}$/cm$^{-1}$): 3422, 1369, 1169, 1090, 802, 740, 687. MS: *m*/*z* (EI) 341.1095 ($M^+$. $C_{19}H_{19}NO_3S$ requires 341.1086), 341, 186, 168, 154, 91. Mp: 132–133 °C.

**(*E*)-3-(*N*-Benzylindol-7-yl)-1-chloro-but-2-ene (11b).** Diethyl chlorophosphate (0.060 ml, 0.40 mmol) was added dropwise to a 0 °C solution of **10b** (100 mg, 0.31 mmol) and pyridine (0.10 ml, 1.2 mmol) in dichloromethane (5 ml), the reaction was stirred at room temperature for 2 hours. Then the mixture was diluted with diethyl ether (10 ml) and $H_2O$ (10 ml), extracted with diethyl ether (3 × 10 ml) and dried ($MgSO_4$). Column chromatography (ethyl acetate/heptane 1 : 1) afforded 71 mg (77%) of the desired product as a pale brown oil.

$^1$H NMR ($CDCl_3$) $\delta$ 7.60 (dd, $J$ = 6.7, 1.2 Hz, 1H), 7.25 (m, 3H), 7.10 (m, 2H), 6.86 (m, 3H), 6.63 (d, $J$ = 3.2 Hz, 1H), 5.63 (dt, $J$ = 1.5, 6.7 Hz, 1H), 5.39 (m, 2H), 4.19 (m, 2H), 1.79 (m, 3H). $^{13}$C NMR ($CDCl_3$) $\delta$ 140.8, 139.0, 132.7, 130.8, 130.5, 128.8, 127.3, 126.3, 125.6, 122.3, 121.9, 120.3, 119.5, 102.4, 51.9, 40.8, 19.3. IR (KBr, $\nu_{max}$/cm$^{-1}$): 3426, 3030, 2922, 1420, 1314, 1176, 796, 725. MS: *m*/*z* (EI) 295.1130 ($M^+$. $C_{19}H_{18}ClN$ requires 295.1128), 295, 259, 168, 91.

**(*E*)-3-(*N*-*p*-Toluenesulfonylindol-7-yl)-but-2-en-1-yl diethyl phosphate (12c).** Pyridine (0.10 ml, 1.2 mmol) and diethyl chlorophosphate (0.19 ml, 1.3 mmol) were added to a 0 °C solution of **10c** in dichloromethane (10 ml). The mixture was heated to room temperature and stirred for 20 h and quenched with water (10 ml), extracted with dichloromethane (3 × 10 ml) and the combined organic phases were dried ($MgSO_4$) and evaporated. Column chromatography (ethyl acetate/hexane 1 : 1) afforded 260 mg (93%) of the desired product as a colourless oil.

$^1$H NMR ($CDCl_3$) $\delta$ 7.64 (d, $J$ = 3.7 Hz, 1H), 7.41 (d, $J$ = 8.4 Hz, 2H), 7.39 (dd, $J$ = 7.6, 1.4 Hz, 1H), 7.17. (t, $J$ = 7.5 Hz, 1H), 7.10 (d, $J$ = 8.0 Hz, 2H), 7.04 (dd, $J$ = 7.4, 1.3 Hz, 1H), 6.69 (d, $J$ = 3.8 Hz, 1H), 5.46 (dq, $J$ = 1.4, 6.7 Hz, 1H), 4.75 (t, $J$ = 7.1 Hz, 2H), 4.17 (q, $J$ = 7.1 Hz, 4H), 2.30 (s, 3H), 2.11 (s, 3H), 1.36 (t, $J$ = 7.1 Hz, 6H). $^{13}$C NMR ($CDCl_3$) $\delta$ 144.0, 142.5, 134.7, 133.1, 132.9, 130.6, 129.3, 126.6, 124.1, 122.6, 122.4, 120.5, 111.1, 64.2, 64.1, 63.7, 63.6, 21.4, 18.9, 16.1, 16.0. IR (KBr, $\nu_{max}$/cm$^{-1}$): 3448, 2984, 1371, 1271, 1176, 1032, 802, 682. MS: *m*/*z* (EI) 477.1359 ($M^+$. $C_{23}H_{28}NO_6PS$ requires 477.1375), 477, 258, 168, 99.

In addition the corresponding chloride (*E*)-3-(*N*-*p*-toluenesulfonylindol-7-yl)-but-2-en-1-chloride was isolated (6 mg, 0.02 mmol, 3%).

$^1$H NMR ($CDCl_3$) $\delta$ 7.63 (d, $J$ = 3.7 Hz, 1H), 7.41 (d, $J$ = 8.2 Hz, 2H), 7.40 (dd, $J$ = 7.8, 1.3 Hz 1H), 7.18 (t, $J$ = 7.5 Hz, 1H), 7.11 (d, $J$ = 8.0 Hz, 2H), 7.04 (dd, $J$ = 7.4, 1.3 Hz, 1H), 6.69 (d, $J$ = 3.7 Hz, 1H), 5.48 (tq, $J$ = 7.7, 1.4 Hz, 1H), 4.26 (d, $J$ = 7.5 Hz, 2H), 2.30 (s, 3H), 2.15 (d, $J$ = 1.2 Hz, 3H).

**(*E*)-1-Acetyloxy-3-(*N*-benzylindol-7-yl)-but-2-ene (13b).** Pyridine (0.090 ml, 1.1 mmol) and acetic anhydride (0.10 ml, 1.0 mmol) were added to a solution of **10b** (203 mg, 0.73 mmol) in dichloromethane (5 ml) and stirred for 24 hours at room temperature. The reaction mixture was quenched with $H_2O$ (5 ml) and dichloromethane (5 ml), extracted with dichloromethane (3 × 10 ml) and the combined organic phases were dried ($MgSO_4$) and evaporated. Column chromatography (ethyl acetate/heptane 2 : 3) afforded 210 mg (90%) of the desired product as a pale brown oil.

$^1$H NMR ($CDCl_3$) $\delta$ 7.63 (dd, $J$ = 1.2, 7.9 Hz, 1H), 7.32–7.22 (m, 3H), 7.15–7.07 (m, 2H), 6.86 (dd, $J$ = 1.2, 7.2 Hz, 1H), 6.77 (m, 2H), 6.65 (d, $J$ = 3.2 Hz, 1H), 5.55 (dt, $J$ = 1.5, 6.9 Hz, 1H), 5.48 (br s, 2H), 4.72 (br s, 2H), 2.01 (s, 3H), 1.85 (s, 3H). $^{13}$C NMR ($CDCl_3$) $\delta$ 205.5, 170.3, 139.8, 139.5, 131.1, 130.8, 129.3, 128.6, 127.1, 126.2, 124.8, 122.1, 120.0, 119.4, 102.1, 60.8, 51.4, 20.2, 19.0. IR (KBr, $\nu_{max}$/cm$^{-1}$): 3031, 1739, 1420, 1361, 1313, 1231, 1028, 796, 725. MS: *m*/*z* (EI) 319.1573 ($M^+$. $C_{21}H_{21}NO_2$ requires 319.1572), 319, 244, 168, 154, 91.

**(*E*)-1-Acetyloxy-3-(*N*-*p*-toluenesulfonylindol-7-yl)-but-2-ene (13c).** Pyridine (0.10 ml, 1.2 mmol) and acetic anhydride (0.10 ml, 1.1 mmol) were added to a solution of **10c** (233 mg, 0.68 mmol) in dichloromethane (10 ml) and stirred for 7 hours at room temperature. The reaction was quenched with water (10 ml) and extracted with dichloromethane (3 × 10 ml) and the combined organic phases were dried ($MgSO_4$) and evaporated to give 244 mg (93%) of the desired product as a light yellow oil, which on standing turned into a low melting point solid.

$^1$H NMR ($CDCl_3$) $\delta$ 7.65 (d, $J$ = 3.8 Hz, 1H), 7.42 (d, $J$ = 8.4 Hz, 2H), 7.39 (dd, $J$ = 1.3, 7.7 Hz, 1H), 7.17 (t, $J$ = 7.5 Hz, 1H), 7.11 (t, $J$ = 8.1 Hz, 2H), 7.05 (dd, $J$ = 1.3, 7.5 Hz, 1H), 6.70 (d, $J$ = 3.7 Hz, 1H), 5.43 (tq, $J$ = 6.8, 1.4 Hz, 1H), 4.76 (d, $J$ = 6.9 Hz, 2H), 2.31 (s, 3H), 2.12 (s, 3H), 2.11 (s, 3H). $^{13}$C NMR ($CDCl_3$) $\delta$ 171.0, 144.5, 142.5, 135.0, 133.2, 132.5, 130.6, 129.2, 126.7, 126.7, 124.1, 123.0, 122.1, 120.4, 111.1, 61.4, 21.4, 21.0, 18.9. IR (KBr, $\nu_{max}$/cm$^{-1}$): 3448, 1736, 1375, 1233, 1176, 802, 681. MS: *m*/*z* (EI) 383.1189 ($M^+$. $C_{21}H_{21}NO_4S$ requires 383.1191), 383, 258, 244, 168, 154, 91.

**(*E*)-3-(*N*-Benzylindol-7-yl)-1-methoxycarbonyloxy-but-2-ene (14).** Methyl chloroformate (0.20 ml, 2.6 mmol) was added dropwise to a 0 °C solution of **10b** (380 mg, 1.37 mmol) in pyridine (2 ml) and dichloromethane (2 ml). The ice bath was removed, and stirring was continued at room temperature for 15 h. Dichloromethane (10 ml) and water (10 ml) were added, and extraction with dichloromethane (3 × 10 ml), drying of the combined organic phases ($MgSO_4$), and evaporation followed by column chromatography (ethyl acetate/hexane 1 : 8) afforded 341 mg (74%) of the desired product as a colourless oil.

$^1$H NMR ($CDCl_3$) $\delta$ 7.65 (dd, $J$ = 1.6, 7.9 Hz, 1H), 7.28 (m, 3H), 6.92 (dd, $J$ = 1.5, 7.4 Hz, 1H), 6.89 (d, $J$ = 5.8 Hz, 2H), 6.66 (d, $J$ = 3.2 Hz, 1H), 5.59 (tq, $J$ = 1.4, 7.0 Hz, 1H), 5.49 (d, $J$ = 12.7, 2H), 4.79 (d, $J$ = 5.0 Hz, 2H), 3.80 (s, 3H), 1.87 (s, 3H). $^{13}$C NMR ($CDCl_3$) $\delta$ 156.1, 141.1, 139.1, 132.4, 130.7, 130.4, 129.0, 128.8, 127.4, 126.3, 123.7, 122.5, 120.3, 119.6, 102.5,

64.7, 55.0, 51.8, 19.8. IR (KBr, $\nu_{max}$/cm$^{-1}$): 2955, 1747, 1444, 1314, 1266. 941, 795, 725. MS: *m*/*z* (EI) 335.1514 ($M^+$. $C_{21}H_{21}NO_3$ requires 335.1521), 335, 244, 168, 91.

### β-Methylcinnamyl acetate (19)

Pyridine (1.0 ml, 12 mmol) and acetic anhydride (1.0 ml, 11 mmol) were added to a solution of β-methyl cinnamyl alcohol[19] (300 mg, 2.3 mmol) in dichloromethane (10 ml) and stirred for 12 hours at room temperature. The reaction was quenched with water (10 ml) and extracted with dichloromethane (3 × 10 ml) and the combined organic phases were dried ($MgSO_4$) and evaporated. Column chromatography (ethyl acetate/hexane 1 : 7) afforded the product as colourless oil. (370 mg, 1.9 mmol, 96%). Spectral data were in accordance with those previously published.[28]

### 20 and 21

The synthesis was performed according to the *general procedure for allylic substitutions with alkylcopper reagents (cinnamyl acetate)* using β-methylcinnamyl acetate in dichloromethane at 20 °C.

The spectral data were in accordance with those previously published (**20**[29] and **21**[30])

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