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TETRAHEDRON: *ASYMMETRY*

Remote control by protecting groups in the diastereoselective addition of acetylides to 2-(4-quinolyl)propanol

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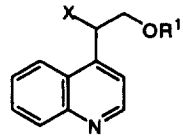
Abstract

Differently *O*-protected 2-(4-quinolyl)propanols undergo, in the presence of chloroformate esters, a regio- and stereoselective addition of acetylides on the carbon α to nitrogen with moderate to good diastereoselectivity. The bulkiness of the OH protecting group, which has a 1,7 relationship with the newly created stereocentre, appears to be mainly responsible for this remote stereocontrol.

Quinolines, together with their hydrogenated derivatives, are components in many natural products.[1] These compounds generally have complex structures and usually only one of the possible stereoisomers is noteworthy for biological activity.



1 X = CH_3
2 X = CH_2OR^2

The stereoselective functionalization of quinolines, having at least one stereogenic centre as a side chain, by nucleophilic addition to an activated heterocyclic system, is still under explored. Only a few examples are known in the literature and they usually involve the nucleophilic addition to a partially rigid ring fused quinoline system, bearing at least two stereogenic centres.[2a,c,d] However, recently Isobe's work, on the synthesis of some Dynemicin A model compounds,[2b] has shown that in the addition to quinolyl derivatives containing only one stereocentre, it is possible to get a good diastereoselection if a suitable combination of various factors affecting the stereochemistry of the reaction is realized.

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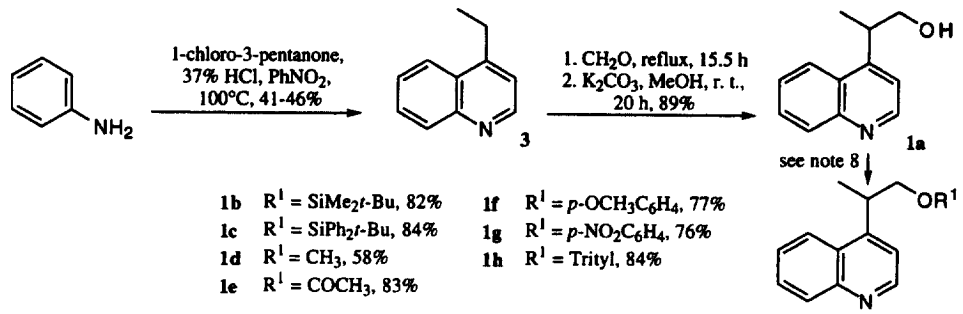
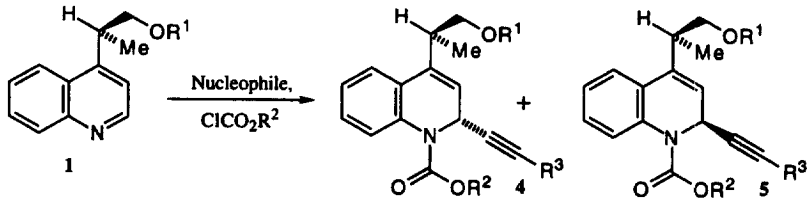
In connection with our interest in the chemistry of enediynes,[3] we recently turned our attention to the synthesis of some Dynemicin A analogues, using **1** and **2** as precursors. For this purpose, following a chemoenzymatic procedure, we recently prepared **2** in both enantiomeric forms.[4] Now, we report our results on the synthesis of racemic **1** and the effect of different factors on the regio- and stereoselectivity with the addition of some acetylides to this substrate. The employed quinolines were synthesized as reported in Scheme 1, starting from 4-ethylquinoline **3**, which was prepared by a modified Skraup procedure.[5,6] Treatment of **3** with formaldehyde gave **1a**,[7] and with the protection of the alcoholic function under varying conditions gave the derivatives **1b–h**.[8]



Scheme 1.

On these compounds we studied the addition of trimethylsilylacetylides in the presence of suitable chloroformate esters (Scheme 2), which enhance the electrophilicity of the heterocyclic ring.[9] We chose first quinoline **1b** and tested the influence of the following variables both on yield and diastereomeric ratio (Table 1): (a) various chloroformates (entries 1–3), (b) various experimental details (order of addition of the reagents, temperature, etc.; entries 3–10), and (c) various counterions of the acetylide (entries 11–12). Although C-4 is also susceptible to nucleophilic attack,[2b] we usually found (except in entry 11) a very regioselective reaction in which the nucleophile attacked **1b** only at position 2 to give a mixture of the stereoisomers **4** and **5** with a moderate diastereomeric ratio. Whatever the protecting group or nucleophile used, it is noteworthy that in all the performed reactions (Tables 1 and 2) diastereomer **4** always prevailed.[10]



Scheme 2.

With the exception of entry 1, for each change in experimental conditions, we did not notice any appreciable influence on the d.r., which was usually in the range 64–68%:32–36%. However, by changing the order of addition of the reagents (see note c in Table 1), only the yield of the reaction was substantially influenced. The best conditions required the sequential addition of nucleophile and chloroformate to a quinoline solution (entry 3) at −78°C, followed by slow warming of the reaction mixture; alternatively, a solution of nucleophile and chloroformate, warmed from −78 to 0°C, can be treated with the quinoline at −78°C (entry 9). The nature of chloroformate (entries 1–3) has an important influence on the ideal reaction temperature, $PhCO_2Cl$ being the best also in terms of diastereomeric ratio. Changing the nucleophile from RMgBr to RMgCl produced an appreciable lowering of the yield (entries 3, 12), while

Table 1
Addition of acetylides to **1b** using different experimental conditions (R^1=$SiMe_2t$-Bu; R^3=$SiMe_3$)

Entry	R^2	Nucleophile	Temperature (°C)	Isolated yield (%)[a]	4 : 5[b]
1	Bn	$SiMe_3C{\equiv}CMgBr$	-78° → -2°[c]	72 (69)	59 : 41[d]
2	Me	$SiMe_3C{\equiv}CMgBr$	0°[c]	78 (76)	66 : 34
3	**Ph**	**$SiMe_3C{\equiv}CMgBr$**	**-78° → -2°[c]**	**77 (64)**	**68 : 32[d]**
4	Ph	$SiMe_3C{\equiv}CMgBr$	-78°[c]	50 (38)	65 : 35
5	Ph	$SiMe_3C{\equiv}CMgBr$	-78°[c]	44 (32)	64 : 36
6	Ph	$SiMe_3C{\equiv}CMgBr$	-78°[c]	49 (43)	64 : 36
7	Ph	$SiMe_3C{\equiv}CMgBr$	-78° → 0°[c]	57 (44)	65 : 35
8	Ph	$SiMe_3C{\equiv}CMgBr$	-78° → 0°[c]	72 (39)	67 : 33
9	**Ph**	**$SiMe_3C{\equiv}CMgBr$**	**-78° → 0°[c]**	**87 (84)**	**68 : 32**
10	Ph	$SiMe_3C{\equiv}CMgBr$	-78°[c]	66 (63)	67 : 33
11	Ph	$SiMe_3C{\equiv}CCeCl_2$	0°[c]	30 (24)[e]	68 : 32
12	Ph	$SiMe_3C{\equiv}CMgCl$	-78° → 0°[c]	35 (34)	66 : 34

Note: a) since by-products derived from chloroformate are always present and not easy to separate from **4/5**, the yield after purity determination by GLC analysis are reported in brackets; b) determined by GLC (RSL 150 column), if not otherwise specified; c) reaction conditions [for each entry order of addition of reagents was reported (quinoline = a, nucleophile = b, chloroformate = c, temperature and reaction times were reported only if necessary); reactions were performed on 100 mg of **1b**, using 3 molar eq of nucleophile (0.5 M sol. in THF) and 3 molar eq of chloroformate]. *E1*, *E3*, *E4*, *E12*: a+b+c, *E2*: b+a+c (after 10 min), *E5*: a+c+b (after 15 min), *E6*: a+b+c (after 15 min); *E7*: a+c (0°C, 30 min) +b (-78°C), *E8*: b+c (for 15 min) + a; *E9*: b+c (-78° → 0°C, 1.5 hr) +a (-78°C), *E10*: b+a (3 hr) +c, *E11*: b+a+c; d) determined by GC-MS (HP-1 column); e) together with 4-5% products derived from addition of nucleophile on C-4.

Table 2
Addition of various nucleophiles to differently protected quinolines (R^2=Ph, nucleophile= R^3–C≡CMgBr)

Entry	Comp.	R^1	R^3	Temp. (°C)	Isol. yield (%)[a]	4 : 5[b]
1	**1a**	H	$SiMe_3$	-78° → -45°[c]	61 (41)	73 : 27[d]
2	**1c**	$SiPh_2t$Bu	$SiMe_3$	-78° → 0°[c]	56 (41)	70 : 30[d]
3	**1c**	$SiPh_2t$Bu	$SiMe_3$	-78° → -21°[c]	95 (86)	69 : 31[d]
4	**1d**	Me	$SiMe_3$	-78° → -14°[c]	76 (73)	67 : 33[e]
5	**1e**	COMe	$SiMe_3$	-78°[c]	80 (69)	61 : 39[d]
6	**1f**	p-OMe-C_6H_4	$SiMe_3$	-78° → -30°[c]	75 (73)	70 : 30[e]
7	**1g**	p-NO_2-C_6H_4	$SiMe_3$	-78° → -35°[c]	88 (82)	75 : 25[d]
8	**1h**	**Tr**	**$SiMe_3$**	**-78°[c]**	**77 (76)**	**87 : 13[d,f]**
9	**1h**	**Tr[g]**	**$SiMe_3$**	**-78°[c]**	**98 (85)**	**84 : 16[d,f]**
10	**1h**	**Tr**	**CH_2OCH_2Ph**	**-78°[c]**	**77[h]**	**84 : 16[i]**
11	**1h**	**Tr**	**$CH_2OCH_2(p$-OMe$)C_6H_4$**	**-78°[c]**	**75[h]**	**84 : 16[j]**

Note: a) see note a), Tab. 1; b) in all cases 4 prevailed and this was proved by chemical correlation between the obtained products; c) see note c), Tab. 1: *E1*, *E3-E11*: a+b+c, *E2*: a+c (0°C, 30 min) +b (-78°C); d) determined by HPLC (Herbasil column); e) determined by GLC (RSL 150 column); f) d.r. determined more precisely after Tr removal (p-TSA, MeOH) to give the corresponding alcohol; g) this reaction was performed on a preparative scale (14 mmol); h) after removal of Tr; i) determined by ^{1}H-n.m.r.; j) determined by ^{13}C-n.m.r.

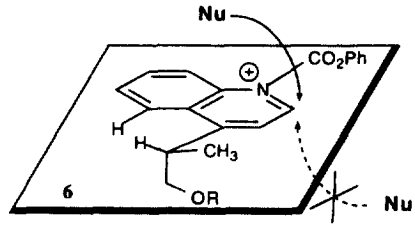
using the corresponding cerous acetylide (entry 11) we obtained not only a very low yield in addition products, but we observed also a certain quantity of the regioisomers derived from nucleophile addition on C-4.

In order to test the scope of this reaction we examined the influence of the hybridization of the attacking carbon, using sp^2 and sp^3 nucleophiles, such as vinylmagnesium bromide and ethylmagnesium bromide. In both cases the reaction was very sluggish and we obtained only small amounts of addition products.

Moreover, in the second case, we isolated also small amounts of products arising from addition to C-4, which slowly decomposed to give the starting compound **1b**.

Since we were not satisfied by the extent of the chiral induction, we studied under experimental conditions equivalent to the ones reported in entry 3 (Table 1), the influence of different protecting groups on the primary alcoholic function. The results are reported in Table 2. Except for **1e** (entry 5), which gave a decreased d.r. compared to **1b**, or for **1d** (entry 4), in all other cases (entries 1–3, 6–11) we found an increase in stereoselectivity, with the triphenylmethyl as protecting group giving the best results.

It is not easy to rationalize the influence of the protecting group: while in the case of TBDPS or trityl groups the increase of diastereoselection can be attributed to the greater bulkiness, the induction observed with **1a** (in this case the reaction must occur on the alcoholate, due to the presence of an excess of acetylide) or **1d** can hardly be explained in terms of just steric hindrance. Moreover, anisyl or *p*-nitrophenyl groups gave an enhanced induction. Thus, it is likely that stereoelectronic effects are also operating. The stereochemical outcome of the addition reaction, together with forcefield calculations performed with Chem 3D Plus from CSC on a simplified analogue of **1b** (R=$SiMe_3$), suggest that the 'H-inside' conformation **6** (with the benzylic hydrogen directed through the *peri* hydrogen) with the nucleophile attacking preferentially from the opposite side to CH_2OR could represent a reasonable model of the transition state (Scheme 3). The bulkiness of the alcohol protecting group is probably responsible for the enhanced induction observed in entries 8–9 and the use of different acetylides (entries 10–11) do not seem to affect in an appreciable way the yield or diastereoselection. Thus, the two stereocentres in **4** being in a 1,4 relationship and the *O*-protecting group in the side chain and the new created stereocentre in a 1,7 relationship, this reaction represents a further interesting example of long-range stereocontrol.[11] It is noteworthy that although the control of diastereoselectivity achieved in this study is not excellent (up to ca. 7:1), simple crystallization of the diastereomeric mixture derived from **1h** (entry 9), allowed us to increase this ratio to 99:1. This result is particularly interesting in view of a possible utilization of these intermediates in the synthesis of Dinemycin A analogues. Studies in this field are now in progress in our laboratories.



Scheme 3.

Acknowledgements

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6. All new compounds quoted in this communication were fully characterized by ^{1}H-NMR, ^{13}C-NMR (in most cases), IR, GC–MS (when feasible).
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8. **1b,c**: R_2t-BuSiCl, imidazole, DMF, r.t.; **1d**: NaH, MeI, THF, r.t.; **1e**: Ac_2O, Py, r.t.; **1f,g**: ArOH, PPh_3, DEAD, CH_2Cl_2, r.t.; **1h**: TrCl, Py, CH_2Cl_2, r.t.
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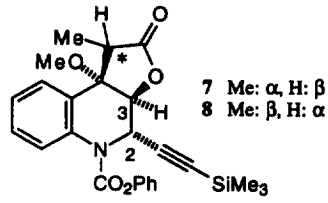
10. Compounds **4** and **5** were transformed into lactones **7** and **8** respectively. [a. *m*-CPBA, CH_2Cl_2, r.t., 92 and 90%; b. *p*-TSA, MeOH, r.t., 60 and 51%; c. TPAPP, NMO, CH_2Cl_2, r.t., 62 and 61%] This route has most likely maintained the configuration of the two original stereogenic centres. The *trans* relationship between H_2 and H_3 was unambiguously established by *J* values in the proton spectrum of the diols that are precursors of **7**, **8** (9.4 and 7.7 Hz respectively). Comparing the ^{1}H-NMR spectra of **7** and **8** we observed in **7** a strong upfield shift (2.52 vs. 3.15) for H α to C=O and in **8** a strong upfield shift (0.77 vs. 1.22) for CH_3 α to C=O. These facts can be explained by the shielding effect of the aromatic ring on the groups positioned over it (H in **7**, CH_3 in **8**). Moreover NOEDIF experiments showed a positive NOE effect between H_3 and CH_3 α to C=O in **7** and between H_3 and H α to C=O in **8** while a strong NOE effect was observed between OCH_3 and H_3 in both stereoisomers. These data agree also with the conformation predicted by force field calculations and allowed us to assign unambiguously the relative configuration of all the stereocentres in **7** and **8**. Further details will be given in a forthcoming full paper.



7 Me: α, H: β
8 Me: β, H: α

11. As a recent review in this field see: Thomas, E. J. *J. Chem. Soc., Chem. Commun.* **1997**, 411–418.