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Asymmetric synthesis of 1,2- and 1,4-dihydroquinolines

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Abstract

Asymmetric synthesis of dihydroquinolines by addition of organometallic reagents on a chiral 3-quinolinyl aminal was studied. 1,2-Adducts were obtained with good regio- and diastereoselectivity. The absolute configuration for 1,2-adducts was determined by X-ray analysis and for 1,4-adducts by chemical correlation. © 1999 Published by Elsevier Science Ltd. All rights reserved.

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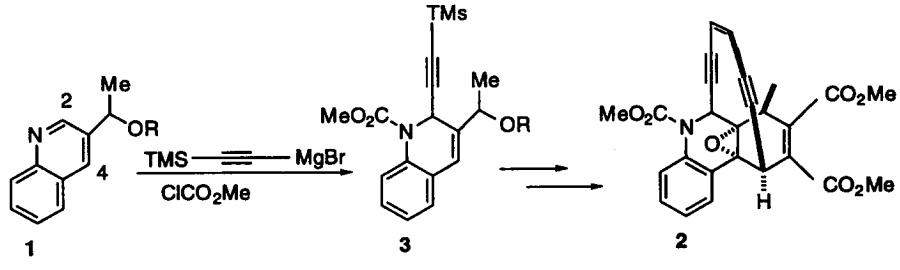
Dynemicin A is a hybrid antitumor antibiotic substance of the enediyne class, and several of the synthetic approaches involve a 1,2-addition of an acetylenic derivative on a substituted quinoline.[1] Takahashi has reported the synthesis of a dynemicin A model **2** from the 2,3-disubstituted dihydroquinoline **3**, obtained by a 1,2-addition of magnesium acetylide on the quinoline **1** in the presence of methyl chloroformiate (Scheme 1).[2]



Scheme 1.

By analogy to our previous work on pyridine aminal,[3] we have decided to study an asymmetric version of this reaction, starting from chiral aminal **4**, easily prepared from aldehyde **5** and (*S,S*)-*N,N*-dimethyl-1,2-diphenylethylene-1,2-diamine[4] in refluxing toluene in the presence of 10% of PPTS (Scheme 2). In

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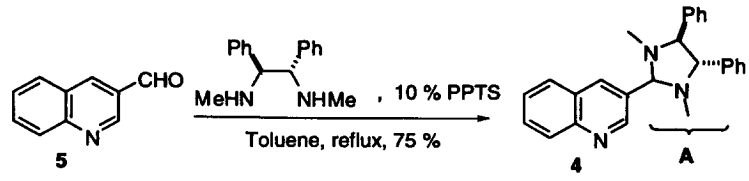
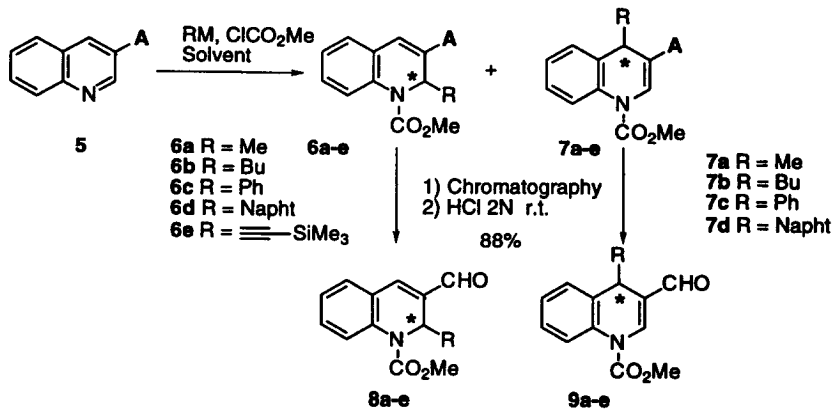
this communication, we wish to report our results concerning the addition, on **4**, of various organometallic reagents in the presence of methylchloroformiate (Scheme 3).[5]



Scheme 2.



Scheme 3.

We first observed a large decrease of the quinolinium salt (formed with the methylchloroformiate) reactivity as compared to the corresponding pyridinium salt. Indeed, addition of organometallic derivatives (Grignard reagents, Grignard reagents in the presence of 10% mol CuI or stoichiometric organocopper reagents, in ether or THF) occurred only at higher temperature (>+5°C), whereas the same reaction on acylpyridinium salt was completed within a few minutes at –78°C.[3]

As shown in Table 1 (entries 1–5), Grignard derivatives (6 equiv.) afforded regioselectively 1,2-adducts **6a–e** (Scheme 3). The best 1,2-regioselectivity (98/2) was obtained with the magnesioacetylide reagent (entry 5, Table 1). In the presence of 10% of copper salt (entries 7–10), a slight 1,4-selectivity was observed while no increase of this selectivity was observed with stoichiometric organocopper reagents (entries 11 and 12). These results strongly contrast with the high 1,4-selectivity usually observed with the pyridine derivatives.[3] The use of organozinc reagent (entry 6) offered only poor 1,2-selectivity.

The crude aminals **6a–c** (Table 1) were purified by column chromatography. Each of them could be isolated as pure diastereomers except for **6e** which was obtained as a mixture of the two diastereomers. They were then hydrolyzed into the aldehydes **8a–e**. The crude mixtures obtained in entries 7–10 (Table 1) were directly submitted to acidic hydrolysis to give a mixture of regioisomers **8a–d** and **9a–d** (Scheme 3). At this point, aldehydes **9a–d** were purified and isolated as a mixture of enantiomers. These aldehydes were then converted into the corresponding aminals by using (*R,R*)-*N,N*-dimethyl-1,2-diphenylethylene-1,2-diamine in refluxing toluene. It was therefore possible to determine, by ^{1}H NMR, the diastereomeric purity of the crude **6a–e** and **7a–d**.

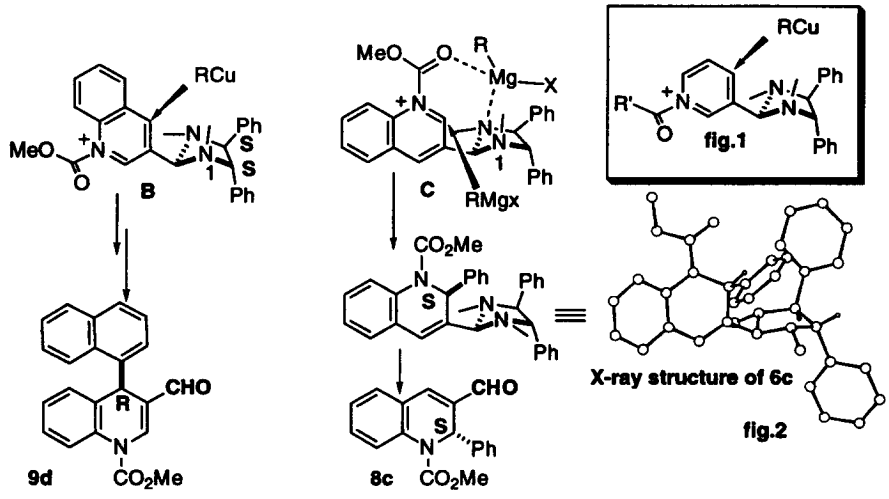
When R was an alkyl substituent (entries 1, 2, 6–8 and 11), the diastereomeric excess of 1,2-adducts **6a–e** varied from low to moderate (20–56%). The best selectivity was observed with BuZnBr (entry 6, de=86%). With unsaturated substituents, a very high stereoselectivity (80–100%) (entries 3–5) was observed for Grignard reagents (compare entries 9, 10 and 12). The diastereomerically pure **6c** (Table 1,

Table 1
Addition of organometallic reagents on **4** in the presence of MeOCOCl

Entry	RM	solvent, temp.	yield (6+7)	Ratio 6:7[a]	6 de[a] (%)	7 de[a] (%)
1	CH_3MgBr	Et_2O, 20°C	83	**6a/7a** = 95:5	33	-
2	BuMgBr	Et_2O, 20°C	73	**6b/7b** = 67:33	20	-
3	PhMgBr	THF, 20°C	70	**6c/7c** = 90:10	100	-
4	NaphtMgBr	THF, 20°C	68	**6d/7d** = 95:5	100	-
5	TMS—≡—MgBr	THF, 20°C	67	**6e/7e** = 98:2	80	-
6	BuZnBr	THF, 20°C	78	**6b/7b** = 60:40	86	-
7	CH_3MgBr (10% CuI)	THF, 5°C	85	**6a/7a** = 30:70	53	4
8	BuMgBr (10% CuI)	THF, 5°C	87	**6b/7b** = 40:60	33	54
9	PhMgBr (10% CuI)	THF, 5°C	94	**6c/7c** = 43:57	53	28
10	NaphtMgBr (10%CuI)	THF, 5°C	78	**6d/7d** = 35:65	50	20
11	CH_3Cu	THF, 20°C	89	**6a/7a** = 40:60	56	20
12	PhCu	THF, 20°C	92	**6c/7c** = 40:60	60	22

a) The regio-(1,4 or 1,2) and diastereoselectivity were determined by ^1H NMR (400 MHz).

entry 3), $[\alpha]_D^{20}$=196 (*c* 0.8, $CHCl_3$), was crystalline. The absolute configuration of the new stereogenic center, determined by X-ray analysis, was shown to be *S*, starting from the aminal (*S,S*)-**4** (Scheme 4 and inset (Fig. 2)). We assumed that all major diastereoisomers **6a,b,d,e** (Table 1, entries 1, 2, 4 and 5), also had the same absolute configuration. Indeed, all the enantiopure aldehydes **8a–d** (**8e** had an ee of 80%) also had the same sign of optical rotation (Table 2, entries 1 and 5).



Scheme 4.

By analogy with reported data[6] for aldehyde **9d** (Table 2, entry 9), we were able to assign the absolute configuration *R* (Scheme 4) to the major enantiomer ($[\alpha]_D^{20}$=–24 (*c* 1.16, $CHCl_3$)). The same stereochemistry was observed for the other aldehydes **9a–c** (Table 2, entries 6–8).

These stereochemical results deserve some comments. If the 1,4-addition, with organocopper reagents, occurs, with a low selectivity, with the same stereochemistry to the one observed with the pyridine aminal

Table 2
Optical rotations of aldehydes **8a–e** and **9a–d**

Entry	R	aldehyde	α_D^{20} (*C*, $CHCl_3$)	ee[a] %
1	Me	**8a**	+306 (*3.1*)	100
2	Bu	**8b**	+346 (*0.45*)	100
3	Ph	**8c**	+551 (*0.65*)	100
4	Napht	**8d**	+387 (*0.55*)	100
5	TMS—≡	**8e**	+362 (*1.0*)	80
6	Me	**9a**	-26 (*0.94*)	4
7	Bu	**9b**	-172 (*0.87*)	54
8	Ph	**9c**	-51 (*0.59*)	28
9	Napht	**9d**	-24 (*1.16*)	20

a) Determined by ^1H NMR (400 MHz) of the corresponding aminal.

(Scheme 4 inset (Fig. 1)),[6] (a *S,S* aminal yields a 1,4-adduct of *R* configuration), the stereochemistry of the 1,2-addition of Grignard derivatives is opposite (a *S,S* aminal yields a 1,2-adduct of *S* configuration) (Scheme 4 inset (Fig. 2)). A possible explanation of these results involves an addition of the organometallic reagents always from the side of N_1-methyl axial substituent on both conformers **B** or **C** (Scheme 4). Conformer **B** would be favored in the presence of organocopper reagents[3] whereas conformer **C** would be favored in the presence of Grignard derivatives (Scheme 4).[7]

In summary, chiral 1,2-dihydroquinolines were easily prepared by addition of Grignard reagents on quinoline aminal **4**. The diastereoselectivity of the reaction was good to excellent for aryl or alkynyl substituents and poor for alkyl substituents. The 1,4-dihydroquinolines were obtained with both lower regio- and diastereoselectivities. Nevertheless, such a strategy would allow an easy access to dynemicin A model **3** from compound **6e**. Work is in progress in our laboratory to improve this methodology.

Acknowledgements

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References

1. Magnus, P.; Eisenbeis, S. A.; Fairhust, R. A.; Iliadis, T.; Magnus, N. A.; Parry, D. *J. Am. Chem. Soc.* **1997**, *119*, 5591–5605; Matthew, D.; Yoon, T.; Danishefsky, S. *J. Angew. Chem.* **1995**, *107*, 1883–1885; Matthew, D.; Yoon, T.; Mosny, K. K.; Chou, T. C.; Danishefsky, S. *J. Am. Chem. Soc.* **1996**, *118*, 9509–9525; Nishikawa, T.; Yoshikai, M.; Obi, K.; Isobe, M. *Tetrahedron Lett.* **1994**, *35*, 7997–8000.
2. Takahashi, T.; Sakamoto, Y.; Yamada, H.; Usui, S.; Fukazawa, Y. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 1345–1348.
3. Mangeney, P.; Gosmini, R.; Raussou, S.; Commerçon, M.; Alexakis, A. *J. Org. Chem.* **1994**, *59*, 1877–1888.
4. Alexakis, A.; Aujard, I.; Mangeney, P. *Synlett* **1998**, 873–874; Alexakis, A.; Aujard, I.; Mangeney, P. *Synlett* **1998**, 875–876; Alexakis, A.; Aujard, I.; Mangeney, P. *Organic Synthesis* **1998**, *76*, 23–25.
5. For addition of organometallic reagents on acylquinolinium salts, see: Otsuji, Y.; Yutani, K.; Imoto, E. *Bull. Chem. Soc. Jpn.* **1971**, *44*, 520; Meyers, A. I.; Natale, N. R.; Wettlaufer, D. G. *Tetrahedron Lett.* **1981**, *22*, 5123–5126; Magnus, P.; Fortt, S. M. *J. Chem. Soc. Chem. Commun.* **1991**, 544–546; Wee, A. G. H.; Liu, B.; Zhang, L. *J. Org. Chem.* **1992**, *57*, 4404–4414; Wu, M. J.; Lin, C. F.; Chen, H. T.; Duh, T. H.; Wang, S. S.; Hsu, S. C. *Bioorg. Med. Chem. Lett.* **1996**, *6*, 2183–2186.
6. Meyers, A. I.; Wettlaufer, D. G. *J. Am. Chem. Soc.* **1984**, *106*, 1135–1136.
7. Alexakis, A.; Lensen, N.; Tranchier, J. P.; Mangeney, P.; Feneau-Dupont, J.; Declerc, J. P. *Synlett* **1995**, 1038–1050.