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A new diastereoselective approach to simplified Dynemicin analogues

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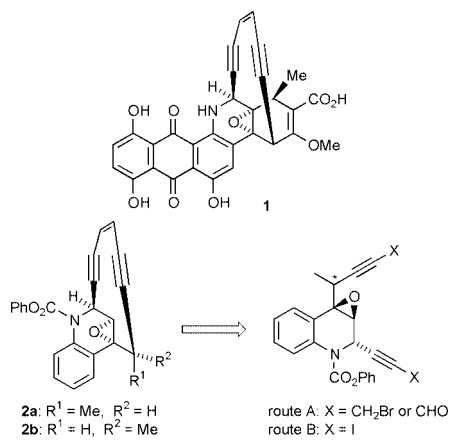
The stereoselective synthesis of new simplified Dynemicin analogues is reported: key steps of the sequence are the regio- and diastereo-selective functionalization of a quinoline nucleus, bearing a substituent with a stereogenic centre, and the formation of the 10-membered cyclic enediyne system by Pd-catalyzed Stille-like reaction.

Enediynes constitute an important family of recently discovered natural derivatives. Owing to their unusual molecular structure and strong cytotoxic activity, *via* unique double strand cleavage of DNA, in recent years these compounds have attracted the attention of many research groups. Dynemicin A **1** is certainly one of the most representative examples of this class of substances and the synthesis of this enediyne has been reported.[1] However, since its molecular structure is complex, many efforts have been made to synthesize simplified analogues, hopefully mimicking the activation mechanism.[2]

We recently performed a regio- and diastereo-selective nucleophilic addition of magnesium acetylides onto 2-(4-quinolyl)propan-1-ol and showed that the extent of induction was determined by the nature of the hydroxy protecting group.[3] Based on this methodology, compounds such as **5** and **6** (see Scheme 2) could be prepared in high chemical yield and moderate to good diastereomeric ratio.

Within our project in the enediyne field,[4] we planned to transform these adducts into enediynes **2a**,**b**, which are simplified analogues of **1** (Scheme 1). Although compounds with similar structure have been recently prepared by Isobe and coworkers,[5] we focused our attention on a completely different synthetic approach. The most critical step of our plan was undoubtedly the formation of the 10-membered cyclic enediyne system. For this purpose two different strategies were envisaged: (1) route A, in which the acyclic system already bears all the required ten carbon atoms; in this case the ring closure could be induced by the base-induced coupling of a bis(propargyl bromide)[6] or by an intramolecular pinacol coupling performed on a bis(aldehyde);[4b] (2) route B, in which the acyclic system, bearing only eight carbon atoms of the incoming enediyne, is coupled with a suitable two-carbon unit.[1a,7]



Scheme 1

We first explored route A. For this purpose, after deprotection of the alcoholic function of **5** (R^1 = TBDMS) and **6** (R^1 = triphenylmethyl (Tr)), obtained as 68:32 and 87:13 diastereomeric mixtures respectively, and chromatographic separation of the epimeric **7a** and **7b**, we separately transformed them into the diacetylenic intermediates **11** and **12**, following the procedure reported in Scheme 2. Owing to the propensity of **8a**,**b** to epimerize, the oxidation of the primary alcoholic function to the aldehyde was troublesome, either under Dess–Martin conditions, which were successfully used for the preparation of enediyne intermediates,[8] or under standard Swern conditions. Finally, we succeeded in performing the reaction under slightly modified Swern conditions[9] and **8a**,**b** were used just after aqueous work-up. The homologation of the aldehyde function of **8a** was first attempted through the one-pot sequence proposed by Ohira,[10] which directly allowed the preparation of **11a** in quite good yield (59%), but with extended epimerization, leading to a 7:3 mixture of **11a** and **11b**, probably due to the basic reaction conditions. We then examined the possibility to utilize the Corey–Fuchs[11] procedure. While the preparation of dibromides **9a**,**b** was realized without problems, the transformation of them to give alkyne moieties was more difficult than expected: after many attempts, in which all the possible factors affecting this transformation were examined, the optimal conditions were found to be treatment of **9a**,**b** with Bu^nLi for 15 min at low temperature under argon; on the other hand, working under nitrogen, the reaction was sluggish and the isolated yields of **10a**,**b** were never higher than 40%! C-Desilylation under basic conditions gave **11a**,**b**, and the overall chemical yield from **7a**,**b** was higher (72 and 76% respectively) than that obtained by the previously attempted one-step sequence and, most importantly, no epimerization was observed. Epoxidation of the double bond to give **12a**,**b** was straightforward and completely stereoselective, as expected from literature data.[5a]

With **10a**,**b**, **11a**,**b** and **12a**,**b** in hand, we tried to perform the homologation of the acetylenic functions. However, all attempts to substitute the acetylenic hydrogens with an alkoxymethyl moiety or a synthetic equivalent were unsuccessful.

At this point we turned our attention to route B and examined the possibility to build the enediynic system through a Stille double coupling reaction. This approach was not straightforward; indeed this methodology has been applied only in a few cases to generate cyclic 3-ene-1,5-diyne systems,[1a,7] but always on partially rigid systems, for which the ring closure should be easier than in our case. For this purpose we prepared the diastereomeric bis(iodides) **13a** and **13b** by simultaneous iodination with *N*-iodosuccinimide/$AgNO_3$[12] of both alkyne functions of **12a**,**b** and then performed the Pd(0)-catalyzed cross-coupling reaction with (*Z*)-bis(trimetylstannyl)ethylene. The first attempts were unsuccessful, but eventually, after a careful optimization of reaction conditions [solvent, temperature, choice of Pd(0) source, use of additives, high dilution in order to minimize intermolecular attack of tin reagent], we were able to obtain the epimeric enediynes **2a**,**b** in satisfactory yields. The different yields (60% for **2a** *cf.* 76% for **2b**)

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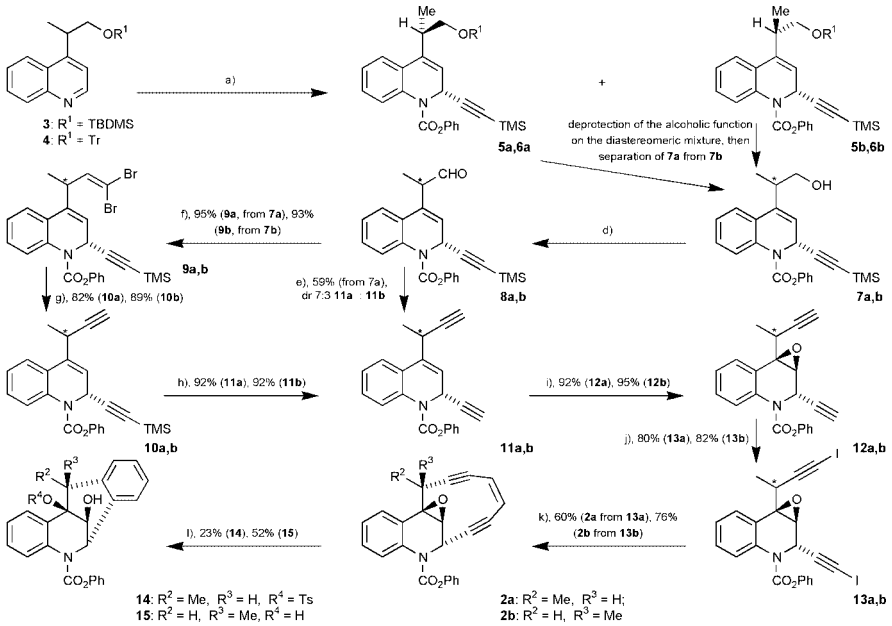

Scheme 2 *Reagents and conditions*: (a) TMS–C≡C–MgBr, $PhCO_2Cl$, THF, −78 °C, R^1 = TBDMS: 87%, 68 : 32 **5a** : **5b**, R^1 = Tr: 98%, 87 : 13 **6a** : **6b**; (b) R^1 = TBDMS: HF, MeCN, −20 → 10 °C, 91%; (c) R^1 = Tr: *p*-TSA, MeOH, 0 °C, 99%; (d) $(COCl)_2$, DMSO, Pr^1_2EtN, −78 °C; (e) $MeCOCN_2P(O)(OMe)_2$, K_2CO_3, MeOH, 0 °C; (f) CBr_4, PPh_3, THF, −78 → −50 °C; (g) Bu^nLi, toluene, −78 °C, Ar; (h) $NaHCO_3$, MeOH, 60 °C; (i) *m*-CPBA, CH_2Cl_2, 0 °C; (j) NIS, $AgNO_3$, THF, r.t., dark; (k) (*Z*)-$Me_3SnCH{=}CHSnMe_3$, $Pd(PPh_3)_4$, LiCl, DMF, 70 °C; (l) i, *p*-TSA (0.5 M sol. in THF), benzene, cyclohexa-1,4-diene, r.t., 30 min; ii, Et_3N, r.t., 24 h.

confirmed our expectations, based on molecular mechanics calculations performed with the CS Chem3D program (Cambridge Soft, Cambridge, MA, USA, version 4.0). For both iodides we found about eight further stable conformations with similar energy, as expected for systems which are not conformationally blocked. The distance between the two iodine bearing sp carbons is in the range 5.0–6.0 Å for **13a** and 4.1–4.4 Å for **13b**. As a result, **13b** is therefore best suited for the new C–C bond forming reaction, owing to the proximity of the two terminal sp carbons.

Finally, we tested the propensity of these compounds to undergo Bergman cycloaromatization, which is responsible for the biological activity of most enediyne derivatives. On Dynemicin and analogues, cycloaromatization usually takes place as soon as the epoxide is opened.[1,2,5*a*,7*a*,13] For this reason we submitted both **2a**,**b** to epoxide opening in the presence of *p*-toluenesulfonic acid.[5*a*,13*a*] To our surprise, after a reaction time of one day, we isolated two different compounds, the monotosylate **14** from **2a** and diol **15** from **2b**, for which the relative configuration at the benzylic carbon is only tentatively assigned based on literature data[5*a*,13*a*] and molecular mechanics studies. At the moment we do not have an explanation for the different behaviour of the two epimers during the acid-induced cycloaromatization process, although we think that different mechanisms could take place, probably due to a different conformation of the molecule in the two epimers.

From our results it seems clear that a relative configuration like that of **7b** seems to be preferable for the synthesis of the enediyne moiety, although this is not the preferred stereoisomer in the initial stereoselective addition step. However, we believe that this is not a real problem, since, thinking to extend our protocol on (*S*)-3-acetoxy-2-(4-quinolyl)propan-1-ol derivatives,[14] the enantiodivergency of this chiral synthon and the diastereodivergency of compounds analogous to **5** and **6** should be exploited to obtain the most useful diastereoisomer for the transformation into the corresponding enediyne. Studies in this field are still in progress in our laboratories.

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