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Asymmetric synthesis of a new simplified dynemicin analogue equipped with a handle

Luca Banfi,* Andrea Basso, Valentina Gandolfo, Giuseppe Guanti and Renata Riva*

Dipartimento di Chimica e Chimica Industriale, via Dodecaneso 31, I-16146 Genova, Italy

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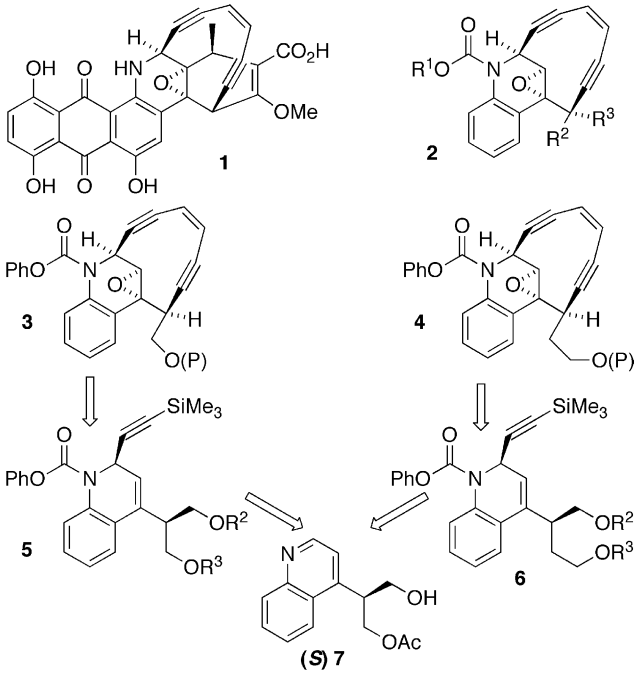
Abstract—The new simplified dynemicin analogue **16** was prepared enantio- and diastereoselectively in 17 steps starting from monoacetate (*S*) **7**. It is equipped with a side arm containing a protected primary alcoholic function ('handle'), which can be used for conjugation with DNA-complexing agents or for devising new types of trigger.

Enediyne antibiotics,[1] such as the calicheamicins[2] and dynemicin A **1**[3–5] are among the most powerful antitumor compounds known. In these substances, the reactive enediyne moiety is stabilized by a structural feature that prevents Bergman cycloaromatization. In the Dynemicins this bias is represented by the *trans* epoxide. A chemical triggering event removes this constraint, unleashing the powerful DNA-cleaving properties of the cyclic enediyne, enhanced by the presence of DNA-complexing substructures (a sort of delivery device). This mechanism of action has attracted the attention of many research groups who devoted their efforts to the rational design of simplified analogues of natural enediynes.[6] We[7] and others[3,8–10] have reported in the past the synthesis of symplified dynemicin analogues of general formula **2**, lacking the quinone moiety, the phenolic hydroxyl group and the cyclohexene ring (Scheme 1). Such compounds showed interesting biological activities, especially when a triggering device was installed onto the nitrogen atom.[7,8,11] However, some drawbacks were found in the simplified molecules, since in natural Dynemicins the quinone moiety not only acts as a trigger, but it also favors complexation with DNA. Its absence may therefore be deleterious for the overall biological activity.



Scheme 1.

In this communication we wish to report our efforts to prepare dynemicin analogues provided with additional functional groups ('handles') that could act as linkers for DNA-complexing substructures. So far, analogues **2** have been prepared without easily derivatizable additional functionalities. Therefore we have designed compounds **3** and **4**, equipped with a protected primary alcohol on a side arm. The varying lenght of the aliphatic chain was planned also to explore triggering devices alternative to the carbamate moiety.

Keywords: Enediynes; Dynemicin; Quinoline; Corey–Fuchs reaction.
* Corresponding authors. Tel.: +39-0103536119; fax: +39-0103536118; e-mail addresses: banfi@chimica.unige.it; riva@chimica.unige.it

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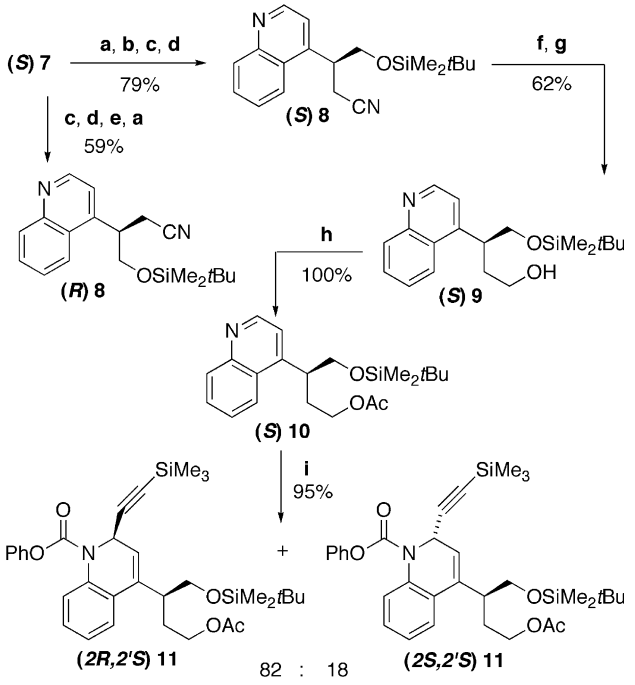
Our efforts have been devoted also to the enantioselective synthesis of **3** and **4**, since the efficient complexation with DNA may depend also on the absolute configuration. To the best of our knowledge, there is only one example in the literature[10] of optically active analogues **2**, obtained via resolution of an intermediate of the synthesis. Our approach starts from monoacetate **7**, easily accessible on large scale by an efficient chemoenzymatic methodology.[12]

The key step for the synthesis of **3** is the protecting group controlled addition of trimethylsilylacetylide to asymmetrically diprotected 2-(4-quinolyl)-1,3-propanediols. The stereochemical course of this reaction was already reported by us.[13] However, all the attempts to convert a series of dihydroquinolines **5** into **3** have failed so far.[14]

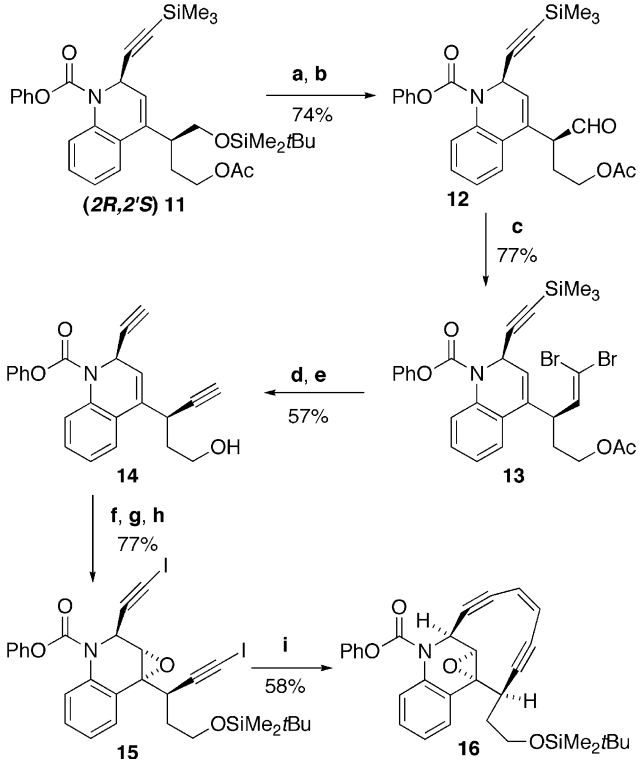
Thus we turned our attention to the synthesis of dynemicin analogues **4**, provided with a longer side arm. The choice of protecting groups for the two alcoholic moieties was crucial in order to achieve a good long-range stereocontrol during acetylide addition onto the quinoline ring. After a thorough investigation[14] we selected compound **10**, having an acetyl group on the longer arm and a Me_2tBuSi group on the shorter one, as optimal substrate (Scheme 2). This compound was straightforwardly obtained from (*S*) **7** in seven steps (49% overall yield) through the nitrile (*S*) **8**.[15] Thanks to the latent symmetry in **7**, also the enantiomer (*R*) **8** could be prepared in the same number of steps, opening an easy entry to the enantiomers of **4**. The absence of racemization in these two routes was demonstrated by Mosher's ester analysis on the alcohol **9**.

The ensuing synthetic steps have been carried out only on the (*S*) enantiomer of **8**. Addition of the magnesium acetylide onto the quinoline in the presence of phenyl chloroformate[13] proceeded in excellent yield. Moreover the diastereoselectivity was surprisingly high, taking into account the distance between the two stereogenic centers and the moderate steric difference between the two conformationally flexible CH_2OSiMe_2tBu and CH_2CH_2OAc side chains.[16]

The synthesis was continued on the major diastereoisomer (Scheme 3), following a synthetic strategy already employed by us for the synthesis of analogues **2** (R^1 = Ph, R^1, R^2 = Me, H).[7] Removal of the $tBuMe_2Si$ group was followed by modified Swern oxidation. In order to avoid epimerization, it is essential to use Hünig's base, to carry out the reaction at −78 °C and, during work-up, to carefully remove the amine, through an acidic washing, before concentration. The subsequent Corey–Fuchs reaction[17] to give **13** turned out to be more problematic than in our previous synthesis.[7] When, following the standard procedure, the aldehyde **12** was added at −78 °C to a preformed (at 0 °C) mixture of CBr_4 and PPh_3, the reaction did not proceed at temperatures <−20 °C. However on warming up to this temperature, decomposition of the starting material



Scheme 2. (a) $tBuMe_2SiCl$, imidazole, DMF; (b) KOH, MeOH, 0 °C; (c) TsCl, pyridine; (d) KCN, nBu_4NI, DMSO; (e) 0.17 M MeONa, MeOH–THF, 0 °C, 80 min; (f) DIBALH, −70 °C; (g) $NaBH_4$, MeOH −40 → −10 °C; (h) Ac_2O, pyridine; (i) $Me_3SiC{\equiv}CMgBr$, $ClCO_2Ph$, THF, −78 °C.



Scheme 3. (a) HF, CH_3CN–H_2O, 0 °C; (b) $(COCl)_2$, $EtN(iPr)_2$, DMSO, CH_2Cl_2, −78 °C, 14 h; (c) CBr_4, PPh_3, CH_2Cl_2, −78 °C → −40 °C; (d) *n*-BuLi, −78 °C; (e) K_2CO_3, MeOH, 0 °C; (f) $tBuMe_2SiCl$, imidazole, DMF; (g) MCPBA, CH_2Cl_2, *T* amb.; (h) I_2•morpholine, benzene, rt, 46 h; (i) (*Z*) $Me_3SnCH{=}CHSnMe_3$, $Pd(PPh_3)_4$, LiCl, DMF.

took place affording **13** in very low yields. On the other hand we found that, by slowly adding a PPh_3 solution to the mixture of the aldehyde and CBr_4 in CH_2Cl_2 at −78 °C,[18] the reaction was fast, reaching completion below −40 °C and affording the desired adduct in good yield.[19]

Treatment of the vicinal dibromide **13** with *n*-BuLi at −78 °C formed the corresponding alkyne, contaminated by 10–20% of a deacetylated by-product. This mixture was directly treated with K_2CO_3 in methanol, which removed both the acetyl and the trimethylsilyl groups, to give diyne **14** ($[\alpha]_D$ +282.6, *c* 1.2, $CHCl_3$). Reprotection as *t*BuMe$_2$Si ether was followed by completely diastereoselective epoxidation and diiodination of the terminal alkynes. Now the set was ready for the final cyclization, which was successfully accomplished by a modification[7] of the method developed by Danishefsky during his total synthesis of dynemicin A.[5] The new dynemicin analogue **16** ($[\alpha]_D$ +394.2, *c* 1.5, $CHCl_3$) was obtained as a white foam in 5.5% overall yield from (*S*) **7** (17 steps). It is worth noting that the enantiomer of **16** is accessible as well, starting again from (*S*) **7**, but going through (*R*) **8** (Scheme 2). On the other hand the C-2′ epimers may be synthesized from the minor adduct of acetylide addition. However for that synthesis we plan to use a different combination of protecting group that produces a lower diastereoselectivity. Studies toward this goal are in progress and will be reported in a forthcoming full paper.

Acknowledgements

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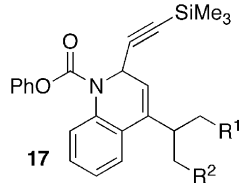
14. Details on this chemistry will be reported in a forthcoming full paper.
15. All new compounds (except for those that were submitted to the next step without a complete purification) were fully characterized by ^{1}H NMR, ^{13}C NMR, GC–MS (when feasible), and elemental analysis.
16. The relative configuration was established by a series of ^{1}H NMR analogies with compounds **17** ($R^1 = H$, $R^2 =$ OSiMe$_2$*t*BuSi, and R^1, $R^2 =$ OR) whose relative configuration was unambigously established.[13] For a general rationalization of the stereochemical course of these additions see our previous paper.[13] Although that model, based only on steric arguments, may well explain the predominance of (2*R*,2′*S*) **11**, the high degree of induction is someway surprising. As a comparison, compound **17** ($R^1 = H$, $R^2 =$ OSiMe$_2$*t*BuSi) gave a 68:32 ratio, whereas compound **17** ($R^1 =$ CH=CH$_2$, $R^2 =$ OSiMe$_2$*t*BuSi) gave only a 60:40 ratio.[14] Since it is hard to consider CH_2OAc smaller than H or CH=CH$_2$, a stereoelectronic effect or an assistance of the OAc group to the nucleophile entrance should be considered.



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19. We believe that different mechanisms are operating in the two cases: when the phosphorane Ph_3P=CBr_2 is preformed, normal Wittig reaction takes place only at temperatures higher than −20 °C. On the other hand, by adding PPh_3 to CBr_4 in the presence of the aldehyde, a different faster mechanism is operating, probably involving an intermediate of phosphorane formation.