Pergamon

Tetrahedron Letters 40 (1999) 7605–7609

TETRAHEDRON
LETTERS

Stereochemical control in the metallohalocarbenoid route to linear enediynes

Justin M. Wright and Graham B. Jones *

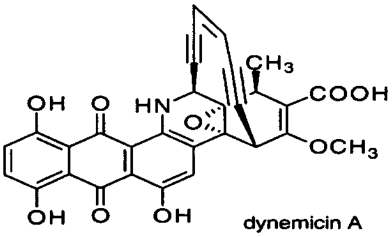
Bioorganic and Medicinal Chemistry Laboratories, Department of Chemistry, Northeastern University, Boston, MA 02115, USA

Received 6 August 1999; accepted 19 August 1999

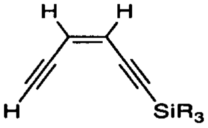
Abstract

Methods for the stereoselective preparation and unmasking of disubstituted Z enediynes are reported. The origins of the unprecedented stereoselectivity of the process are uncovered. © 1999 Elsevier Science Ltd. All rights reserved.

The discovery of the enediyne class of antitumor antibiotics, exemplified by dynemicin A, stimulated considerable interest in the preparation of conjugated (Z) 3-ene-1,5-diynes, and their application in the assembly of both designed and natural enediyne target structures.[1] Interest in these systems is related to their ability to undergo Bergman[2] or Myers[3] type cycloaromatization to yield diyl radicals, which participate in atom transfer chemistry and which are believed to be the origin of the cytotoxic effects of enediynes.[1] These properties, coupled with ongoing clinical trials of enediyne derivatives have spurred interest in general methods for the preparation of linear enediyne building blocks using a variety of different methods.[4] A widely used tactic involves assembly of differentially substituted enediynes **1** allowing regioselective and controlled assembly of the typically labile cyclic enediyne core.



dynemicin A



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Our interest in linear enediynes was fueled by the discovery that propargyl bromide **4** undergoes a rapid coupling–elimination reaction in the presence of LiHMDS to preferentially produce Z enediyne **3** (R=TMS), via the presumed intermediacy of a bromodiyne **5** (Scheme 1).[5] This unexpected result

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* Corresponding author.

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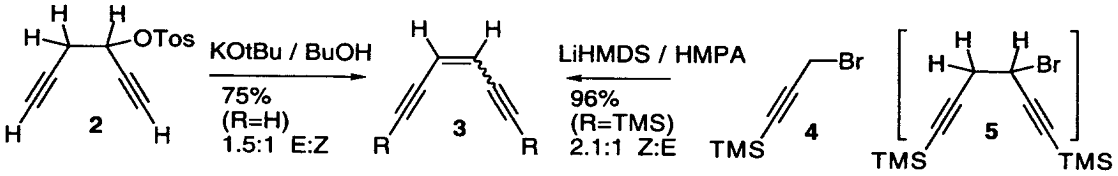
PII: S0040-4039(99)01593-2

contrasts with the work of Sondheimer, who reported that the base induced elimination of the propargyl tosylate **2** preferentially produces the thermodynamically more stable *E*-isomer **3** (R=H).[6] Due to the commercial availability of trialkylsilylpropargylic halides[7] and continued interest in the design of enediyne prodrugs, we elected to scrutinize the process further. Employing 0.25 equiv. of base (THF/–85°C) and terminating the reaction after 5 min, the deliberate interception of bromodiyne **5** was effected (84%).[8] This allowed the stereoselectivity of both the elimination and the in situ coupling–elimination to be investigated as a function of base, temperature and various additives (Table 1). To our surprise, elimination from **5** using LiHMDS gave an inferior *Z*:*E* ratio, although a temperature dependence on this ratio was revealed (entries 1–3). The nature of the base used is also critical, LDA giving no selectivity both in the presence and absence of HMPA. Deliberate introduction of LiBr, which is liberated in the in situ reaction, and which has been reported to stabilize metallohalocarbenoid reactivity,[9] had a restorative effect however (entry 5). Turning our efforts to the in situ coupling–elimination,[5] a clear temperature dependence on stereocontrol is revealed (entries 6–9) but introduction of additional LiBr had a negative impact both on yield and selectivity (entries 10 and 11). Perhaps more surprising still is the observation that high chemical yields are attainable even at ambient temperature (entry 9), challenging the perception that metallohalocarbenoids are unstable, even in the presence of the destablizing agent HMPA.[9]



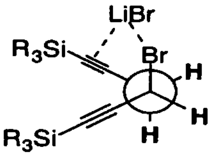
Scheme 1. Direct and in situ elimination strategies for enediyne synthesis

Assuming an antiperiplanar elimination pathway, the predominance of the *Z*-isomeric product is suggestive of a transition state where the alkynyl groups adopt a *syn* orientation, either by responding to repulsive interactions with the incoming base or benefiting from some form of cooperative attractive interaction. These might be manifested either by coordination to the lithium halide **6**, intra-alkynyl attraction **7**, or silyl-base interactions **8**.

Table 1
Stepwise and in situ elimination of propargyl bromides to give enediyne **3** (R=TMS)

Entry	Substrate	Base	Eq.	Temp.	Additives	Yield **3**	Z:E
1	**5**	LiHMDS	1.1	-95	HMPA(1.1)	93	1.6:1
2	**5**	LiHMDS	1.1	-78	HMPA(1.1)	95	1.5:1
3	**5**	LiHMDS	1.1	0	HMPA(1.1)	92	1.2:1
4	**5**	LDA	1.8	-95	HMPA(1.1)	91	1:1
5	**5**	LiHMDS	1.1	-95	HMPA (1.1) LiBr (5)	93	2.2:1
6	**4**	LiHMDS	1.1	-95	HMPA(1.1)	96	2.2:1
7	**4**	LiHMDS	1.1	-45	HMPA(1.1)	94	1.6:1
8	**4**	LiHMDS	1.1	0	HMPA(1.1)	92	1.3:1
9	**4**	LiHMDS	1.1	25	HMPA(1.1)	90	1.2:1
10	**4**	LiHMDS	1.1	-95	HMPA (1.1) LiBr (5)	27	1.5:1
11	**4**	LiHMDS	1.1	-95	LiBr (5)	25	1.5:1
12	**4**	KHMDS	1.1	-95	HMPA (1.1)	92	1.8:1

6



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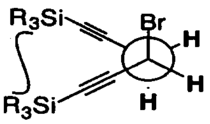

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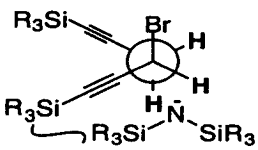
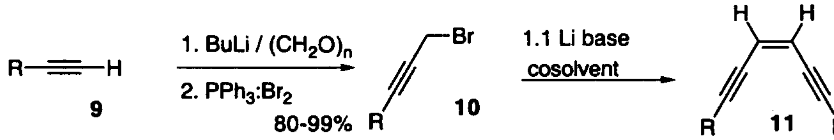
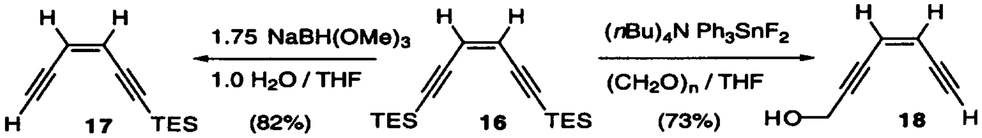


To probe these effects, a series of propargylic bromides **10** were prepared, and subjected to optimized conditions for in situ coupling–elimination (Scheme 2). The procedure gave high yields of desired enediynes **11**, and in each case examined the geometric isomers were readily separable using standard chromatographic methods. Stereochemical outcome of the reactions was indeed sensitive to bulk of the alkyne termini such that the triethylsilyl analog (Table 2, entry 2) was more selective, but additional bulk was detrimental (entries 3–7). Analysis of the TES analogs revealed a strong temperature dependence on selectivity (entries 8–14). The effect of carbenoid destabilizing additives was also scrutinized, and results obtained using the TES group could be duplicated using the HMPA substitute DMPU, and even improved upon by employing the powerful electron donating solvent trispyrrolidinophoramide (TPP) (entries 15–18). Finally, the influence of the base was examined, using a series of lithium disilazide analogs **12**–**15** with the TES substrate (entries 19–24). Subtle changes in selectivity were revealed, with the *n*-alkyl base **12d** proving optimal yet aryl bases **12b** and **14** resulted in *reversal* of selectivity. Conducting the reactions at an even lower temperature (using the TPP additive to prevent precipitation) resulted in even higher selectivity (entry 25). The notion that base/substrate alkylsilyl interactions play a key role in selectivity was boosted further by striking results obtained with alternate substrates (entries 26–28), with up to 12:1 *Z* selectivity attainable with appropriate combinations. These results are significant in that they ***tentatively suggest that appropriately chosen base/substrate combinations can be tailored to allow access to otherwise thermodynamically unfavorable products.***



Scheme 2. Carbenoid coupling–elimination strategy for in situ enediyne synthesis

This stereoselective route to *Z* enediynes can be expected to find application in the preparation of synthetic enediyne antitumor agents. The 1,6 dilithio 3-hexene-1,5-diyne (**11**, R=Li), available via protodesilation and metalation, has previously been used for the construction of enediynes, and we sought to apply *selective* unmasking of the silyl groups to enable sequential elaboration of the termini.[1] Using a stoichiometric modification of the excellent procedure of Myers,[10] monosilylated substrate **17** was produced in 82% yield (Scheme 3). Likewise, deprotective hydroxymethylation using an anhydrous TBAF equivalent in the presence of paraformaldehyde gave **18** in 73% yield.[11]

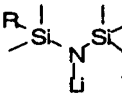


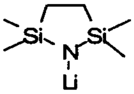
Scheme 3. Selective unmasking and transformation of *Z* enediynes

Thus, the carbenoid route to enediynes, when followed with differential deprotection provides a highly efficient route to enediyne building blocks. A number of syntheses have involved manipulation of enediynes such as **17** and **18**,[1,12] and the method is thus expected to find utility both in the design of second generation enediyne antiproliferative agents, and in the total synthesis of the natural products.[13]

Table 2
In situ elimination of various bromides **10** to give enediynes **11**

Entry	R	Base	Temp.	Additives	Eq.	Yield **11**	Z:E
1	TMS	**12a**	-95	HMPA	1.1	96	2.2:1
2	TES	**12a**	-95	HMPA	1.1	94	4.2:1
3	TBDMS	**12a**	-95	HMPA	1.1	90	4.0:1
4	TIPS	**12a**	-95	HMPA	1.1	92	2.9:1
5	TPS	**12a**	-95	HMPA	1.1	89	1.2:1
6	DMTS	**12a**	-95	HMPA	1.1	91	1.1:1
7	tBu	**12a**	0	HMPA	1.1	25	1.2:1
8	TES	**12a**	-115	HMPA	1.1	88	5.8:1
9	TES	**12a**	-104	HMPA	1.1	91	5.0:1
10	TES	**12a**	-70	HMPA	1.1	94	3.7:1
11	TES	**12a**	-45	HMPA	1.1	92	1.6:1
12	TES	**12a**	-20	HMPA	1.1	95	1.6:1
13	TES	**12a**	-0	HMPA	1.1	89	1.0:1
14	TES	**12a**	25	HMPA	1.1	92	1.0:1
15	TES	**12a**	-95	DMPU	1.1	89	4.0:1
16	TES	**12a**	-95	TPP	1.1	93	4.0:1
17	TES	**12a**	-95	HMPA	5.0	91	4.0:1
18	TES	**12a**	-95	TPP	5.0	95	6.1:1
19	TES	**12b**	-95	HMPA	1.1	87	1:1.6
20	TES	**12c**	-95	HMPA	1.1	91	3.3:1
21	TES	**12d**	-95	HMPA	1.1	90	5.1:1
22	TES	**13**	-95	HMPA	1.1	92	1.8:1
23	TES	**14**	-95	HMPA	1.1	89	1:1.2
24	TES	**15**	-95	HMPA	1.1	94	2.0:1
25	TES	**12d**	-115	TPP	5.0	88	**9:1**
26	TBS	**12d**	-115	TPP	5.0	92	**12:1**
27	TMS	**12d**	-115	TPP	5.0	89	1.8:1
28	TPS	**14**	-95	TPP	5.0	90	1.5:1


12
a R=Me
b R=Ph
c R=*n*Pr
d R=*n*Bu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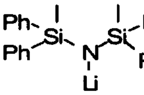
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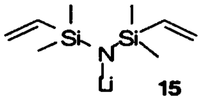
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In summary, examination of the factors governing the stereoselective coupling of propargylic bromides to produce enediynes suggests a strong dependence on developing interactions between the substrate and base. Coupled with deprotective elaboration, this method now provides a high yielding and stereoselective route to functionalized enediyne synthons.

Acknowledgements

We thank the NIH (1RO1GM57123) for generous financial support.

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