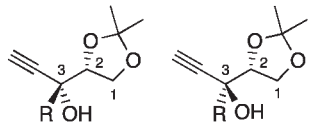
Diastereoselective Additions of Ethynyl Grignard Reagent to Erythrulose Derivatives

Shoji Kobayashi, Parthasarathi Das, Guang Xing Wang, Takashi Mita, Martin J. Lear, and Masahiro Hirama*
Department of Chemistry, Graduate School of Science, Tohoku University and CREST, Japan Science and Technology Corporation (JST), Sendai 980-8578

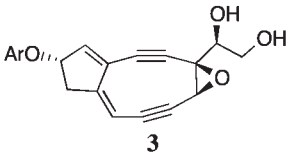
(Received November 30, 2001; CL-011214)

Through systematic changes in reaction conditions and in the use of Ti(O*i*Pr)$_4$, the typical stereochemical outcome of ethynylmagnesium bromide on α,β-*O*-isopropylidene-erythrulose derivatives has been reversed with exceptional levels of control.

During the course of our recent studies into the total and analog synthesis of nine-membered enediyne antibiotics, we have been continuously improving our tactical approach in the synthesis of key fragments. In particular, we have shown 1,2-*O*-isopropyridene-3-ethynylerythrulose derivatives (cf. **1**, **2**, *ent*-**1** and *ent*-**2**) to be valuable intermediates in our synthetic studies of N1999-A2 (**3**), the neocarzinostatin chromophore, C-1027, and model chromophores of kedarcidin.[1]



1 : R= CH_2OH **2** : R= CH_2OH



3

To date only a few methods to obtain **1** and **2** have been reported, especially with regard to attaining 2,3-*syn*-isomers (**1**). Specifically, Nagano[2] and Terashima[3] achieved the synthesis of **1** and **2** by treating ethynyl Grignard reagent or lithium acetylides with ketones **5a** or **5c**, respectively, but no notable selectivity for 2,3-*syn*-products (**1**) over 2,3-*anti*-isomers (**2**) were observed. Although the 2,3-*syn*-selective addition with the corresponding aldehyde (**4**) has been studied extensively[4] and some useful conditions[4b,c] including the use of organocopper reagents[4d] have been reported, these are not always applicable to functionalized ketones or to the low reactivity of ethynyl copper reagents. Indeed, treatment of the TBS-protected ketone (**5b**) with ethynyl copper reagent in THF-Me_2S[4d] resulted in the complete recovery of **5b**. The best cases of organometallic additions to systems like **5** which divert from an *anti*-selective outcome involve carbonyl-substrates with α-benzyloxy or non-cyclic alkoxy protective groups, that are readily capable of forming a strong metal chelate between the ether oxygen and carbonyl groups.[5,6] To the best of our knowledge, only the groups of Nagano[2] and Marco[7] have reported 2,3-*syn*-selective Grignard additions to the cyclic 1,2-*O*-isopropylidenes (**5**), but still the ratios are rather poor.[8] In this letter, we disclose stereodivergent conditions to generate either the *syn*-adducts (**1**) or the *anti*-adducts (**2**) with high levels of stereoselectivity.

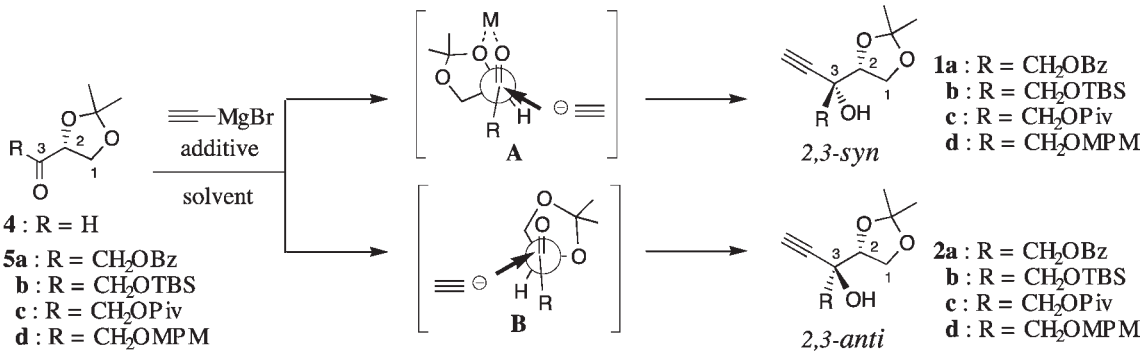
Results of the addition of ethynyl Grignard reagent to the ketones (**5b-d**) are summarized in Table 1. *Anti*-adduct (**2b**) was obtained predominantly in the case of the TBS-ether (**5b**) in various solvents without additives (entry 1–4). Notably, the reaction in THF or Et_2O gave the *anti*-adduct (**5b**) in high yield and selectivity (entry 1, 2). Addition of $ZnBr_2$ and $MgBr_2$•OEt_2 was ineffective in trying to reverse the *anti*-selectivity,[4,9] and only a decrease in both the reaction rate and the chemical yield resulted (entry 5–9). Interestingly, the *syn/anti* ratio changed dramatically in favor of the *syn*-adduct (**1b**) when the reaction was conducted in CH_2Cl_2 or THF in the presence of Ti(O*i*Pr)$_4$ (entry 10, 11).[4b,5a,6a,7b,10] In contrast to that observed for the TBS-ether (**5b**), reactions of the pivalate (**5c**) in the absence of additives gave the *anti*-adduct (**2c**) in poor ratios (entry 12–15); in fact, entry 15 even gave a marginal preference for the *syn*-adduct (*ent*-**1c**). Remarkably, the addition of Ti(O*i*Pr)$_4$ was exceedingly effective in this series, and the reaction in THF solely gave the *syn*-adduct (**1c**) as a single stereoisomer (entry 17), as proved by X-ray crystallography.[11] This marked tendency was also observed with the MPM-ether (**5d**) (entry 18), and all reactions were free from racemization.

Table 1. Reaction of ketones (**5**) with ethynyl Grignard reagent[a]

entry	ketone	solvent	additive[b]	*syn/anti*[c]	yield/%[c]
1	**5b**	THF	none	10 : 90	96[d]
2	**5b**	Et_2O	none	9 : 91	95[d]
3	**5b**	Toluene	none	20 : 80	28
4	**5b**	CH_2Cl_2	none	15 : 85	71
5	**5b**	Et_2O	$ZnBr_2$	13 : 87	20
6	**5b**	CH_2Cl_2–Et_2O (2 : 1)	$ZnBr_2$	21 : 79	12
7	**5b**	Et_2O	$MgBr_2$•OEt_2	19 : 81	10
8	**5b**	CH_2Cl_2–Et_2O (2 : 1)	$MgBr_2$•OEt_2	21 : 79	11
9	**5b**	CH_2Cl_2	$MgBr_2$•OEt_2	18 : 82	63
10	**5b**	CH_2Cl_2	Ti(O*i*Pr)$_4$	80 : 20	76[d]
11	**5b**	THF	Ti(O*i*Pr)$_4$	93 : 7	90
12	**5c**	THF	none	47 : 53	81
13	**5c**	Et_2O	none	28 : 72	78
14	**5c**	Toluene	none	34 : 66	42
15	*ent*-**5c**	CH_2Cl_2	none	55 : 45	97[d]
16	**5c**	CH_2Cl_2	$MgBr_2$•OEt_2	43 : 57	73
17	**5c**	THF	Ti(O*i*Pr)$_4$	*syn* only	93[d]
18	**5d**	THF	Ti(O*i*Pr)$_4$	*syn* only	75[d]

[a]Reactions were performed at −78 °C to −10 °C for 2–4 h in entry 1–9 and entry 12–16, but at −78 °C to room temperature for 1–2 h in entry 10, 11 and entry 17, 18. Ethynylmagnesium bromide (1.5–4.0 equivalents, 0.5 M solution in THF) purchased from Aldrich chemical co., inc. was used. [b]1.5–4.0 equivalents of additives were used. [c]Ratio of *syn*-(**1**)/*anti*-(**2**) and yield were determined on crude by 200 MHz ^{1}H-NMR analysis, unless noted otherwise. [d]Isolated yield after column chromatography.

In summary, we have succeeded in the stereodivergent addition of the acetylide group to ketones (**5**) by simple



Scheme 1. Complementary and highly stereoselective acetylide additions to erythrulose derivatives (**5**) (see Table 1).

modification of the reaction conditions to generate either, the *syn*-adducts (**1**) or, the *anti*-adducts (**2**) with high levels of diastereoselectivity. Arguably, this approach benefits from the fact that the sterically-restricted acetonide group which normally exhibits depressed oxygen-donor abilities relative to acyclic ether oxygens,[6g,7b] can function as a strong chelating group in the presence of $Ti(OiPr)_4$[12] and can thereby direct formation of the *syn*-adduct (**1**) through a five-membered chelation transition state (Scheme 1, **A**).[2,4,7b,8] On the other hand, formation of the *anti*-adduct (**2**) can be rationalized to proceed *via* a non-chelation Felkin-Ahn (Scheme 1, **B**) or β-chelation transition state.[2,4,7b] It is unclear, however, whether the alkyl arm (R) in **5** plays a role in the stereochemical outcome, and other transition states are possible.[2,12] But what is clear is that $Ti(OiPr)_4$ is critical to giving high levels of 2,3-*syn*-selectivity. Since the keto-precursors **5c** and *ent*-**5c** are readily available in multigram quantities from D-isoascorbic acid (6 steps, 41% overall yield)[3,13,14] or L-tartaric acid (7 steps, 31% overall yield),[3,15] respectively, and from the success of our own synthetic endeavors,[1] we anticipate that the enantiopure alcohols **1** and **2** will be of wide utility in synthesis.

This paper is dedicated to Prof. Teruaki Mukaiyama on the occasion of his 75th birthday.

References and Notes

1 a) N1999-A2 (**3**): S. Kobayashi, S. Ashizawa, Y. Takahashi, Y. Sugiura, M. Nagaoka, M. J. Lear, and M. Hirama, *J. Am. Chem. Soc.*, **123**, 11294 (2001). b) Neocarzinostatin and C-1027: I. Sato, K. Toyama, T. Kikuchi, and M. Hirama, *Synlett*, **1998**, 1308. c) Kedarcidin models: S. Kawata, F. Yoshimura, J. Irie, H. Ehara, and M. Hirama, *Synlett*, **1997**, 250; K. Iida and M. Hirama, *J. Am. Chem. Soc.*, **117**, 8875 (1995).

2 H. Nagano, M. Ohno, Y. Miyamae, and Y. Kuno, *Bull. Chem. Soc. Jpn.*, **65**, 2814 (1992).

3 K. Nakatani, K. Arai, N. Hirayama, F. Matsuda, and S. Terashima, *Tetrahedron*, **48**, 633 (1992).

4 For early contributions describing the stereochemical behavior of **4**, see: a) K. Suzuki, Y. Yuki, and M. Mukaiyama, *Chem. Lett.*, **1980**, 1529. b) J. Mulzer and A. Angermann, *Tetrahedron Lett.*, **24**, 2843 (1983); c) D. Horton, J. B. Hughs, and J. K. Thomson, *J. Org. Chem.*, **33**, 728 (1968). d) F. Sato, Y. Kobayashi, O. Takahashi, T. Chiba, Y. Takeda, and M. Kusakabe, *J. Chem. Soc., Chem. Commun.*, **1985**, 1636. d) For a review, see: J. Jurczak, S. Pikul, and T. Bauer, *Tetrahedron*, **42**, 447 (1986).

5 Reviews: a) M. T. Reetz, *Angew. Chem., Int. Ed. Engl.*, **23**, 556 (1984). b) D. M. Huryn, in "Comprehensive Organic Synthesis," ed. by B. M. Trost, I. Fleming, and S. L. Schreiber, Pergamon Press, Oxford (1991), Vol. 1, p 49.

6 For example, see: a) M. Carda, F. González, S. Rodríguez, and J. A. Marco, *Tetrahedron Asymmetry*, **4**, 1799 (1993). b) M. Carda, E. Castillo, S. Rodríguez, F. González, and J. A. Marco, *Tetrahedron Asymmetry*, **12**, 1417 (2001). c) W. C. Still and J. H. McDonald, *Tetrahedron Lett.*, **21**, 1031 (1980). d) D. A. Evans, J. C. Barrow, J. L. Leighton, A. J. Robichaud, and M. Sefkow, *J. Am. Chem. Soc.*, **116**, 12111 (1994). e) E. M. Carreira and J. D. Bois, *J. Am. Chem. Soc.*, **117**, 8106 (1995). f) K. C. Nicolaou, J.-Y. Xu, S. Kim, T. Ohshima, S. Hosokawa, and J. Pfefferkorn, *J. Am. Chem. Soc.*, **119**, 11353 (1997). g) K. Mead and T. L. MacDonald, *J. Org. Chem.*, **50**, 422 (1985).

7 a) M. Carda, F. González, S. Rodríguez, and J. A. Marco, *Tetrahedron Asymmetry*, **3**, 1511 (1992). b) J. A. Marco, M. Carda, F. González, S. Rodríguez, E. Castillo, and J. Murga, *J. Org. Chem.*, **63**, 698 (1998).

8 Only Chikashita et al. have succeeded in the 2,3-*syn*-selective addition of methyllithium to 1,2-*O*-isopropylidene ketones (**5**): H. Chikashita, Y. Nakamura, H. Uemura, and K. Itoh, *Chem. Lett.*, **1992**, 439.

9 a) G. E. Keck, M. B. Andrus, and D. R. Romer, *J. Org. Chem.*, **56**, 417 (1991). b) M. Asami and R. Kimura, *Chem. Lett.*, **1985**, 1221. c) K. T. Mead, *Tetrahedron Lett.*, **28**, 1019 (1987).

10 a) See lead reference: M. T. Reetz and M. Hullmann, *J. Chem. Soc., Chem. Commun.*, **1986**, 1600. b) C. Ferreri, G. Palumbo, and R. Caputo, in "Comprehensive Organic Synthesis," ed. by B. M. Trost, I. Fleming, and S. L. Schreiber, Pergamon Press, Oxford (1991), Vol. 1, p 139.

11 2,3-*Syn*-selective procedure. Under an argon atmosphere, titanium-(IV) isopropoxide (1.37 ml, 4.64 mmol) was added to a suspension of the ketone **5c** (1.08 g, 4.42 mmol) and molecular sieves 4A (powdered, 2.20 g) in THF (14 ml) at −78 °C. [Addition of molecular sieves 4A increased chemical yield, but did not alter *anti/syn* ratio.] The mixture was stirred for 25 min at −78 °C, ethynylmagnesium bromide (0.5 M solution in THF, 26.5 ml, 13.3 mmol) was added and then warmed gradually to room temperature over 1 h. The mixture was quenched with saturated NH_4Cl solution, and standard workup and purification procedures solely afforded alcohol **1c** (1.11 g, 4.11 mmol, 93%), identical in physical data as recorded previously [ref. 3].

12 The group of Reetz observed non-chelation effects for the weakly lewis-acidic methyl- or allyl-titanium reagents, $RTi(OiPr)_3$. But this was both dependent on the substrate and the reagent.[10] Therefore, the actual role of $Ti(OiPr)_4$ in our case with the formation of unknown acetylide species and their attack on ketone **5** in THF is still a matter of debate.

13 E. Abushanab, P. Vemishetti, R. W. Leiby, H. K. Singh, A. B. Mikkilineni, D. C.-J. Wu, R. Saibaba, and R. P. Panzica, *J. Org. Chem.*, **53**, 2598 (1988).

14 Recently, an efficient procedure for the preparation of **5** from L-(*S*)-erythrulose has been reported: M. Carda, S. Rodríguez, J. Murga, E. Falomir, J. A. Marco, and H. Roper, *Synth. Commun.*, **29**, 2601 (1999).

15 K. Fujita, H. Nakai, S. Kobayashi, K. Inoue, S. Nojima, and M. Ohno, *Tetrahedron Lett.*, **23**, 3507 (1982).