A NEW METHOD FOR THE PREPARATION OF PHENYL-SUBSTITUTED *CIS*-ENEDIYNE FROM A PHTHALIDE DERIVATIVE

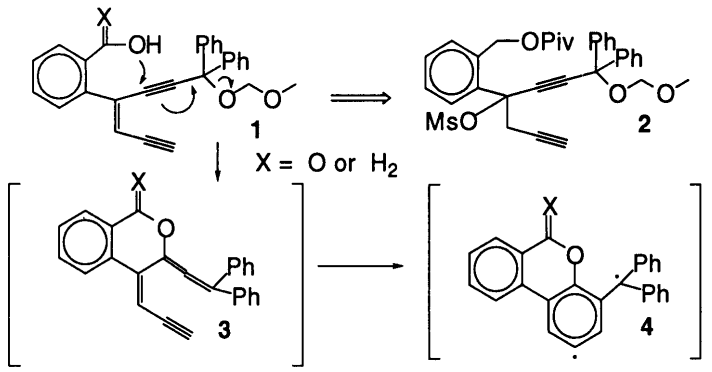
Hisao NEMOTO,* Junya KIKUISHI, and Masayuki SHIBUYA

Faculty of Pharmaceutical Sciences, University of Tokushima, Sho-machi, 1-78, Tokushima 770, Japan

Conversion of the phthalide derivative **5** to the enediynes **6** and **11** are described. Treatment of **5** with 1,8-diazabicyclo[5.4.0]undec-7-ene in hexamethylphosphoric triamide stereoselectively gives **6**, which can be used as an efficient DNA-damaging biradical.

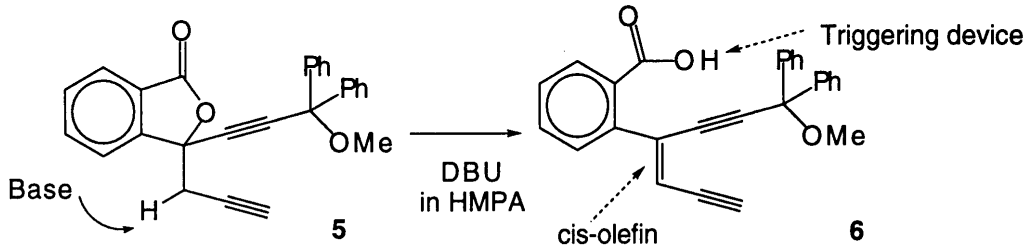
KEY WORDS DNA; biradical; enediyne; Myers-Saito cyclization

Preparation of *cis*-enediyne systems (i.e., **1,** Chart 1) are of importance for the highly efficient generation of DNA-damaging biradicals (i.e., **4**) *via* Myers-Saito cyclization.[1] Recently, we have demonstrated an efficient dehydrotoluene biradical formation reaction of the acyclic enediyne **1** *via* the Myers-Saito cyclization of the enyne-allene intermediate **3** (Chart 1). The cyclization of **1** producing the biradical **4** is based on the generation of the enyne-allene **3** by the intramolecular triggering system which fixes two sp carbon atoms close together.[2] We have prepared **1** by stereoselective formation of *cis*-olefin *via* the elimination of the mesylate intermediate **2**.[2, 3]



(Chart 1)

In this paper, we report a new method for the preparation of the *cis*-enediyne system. The key intermediate is the phthalide derivative **5** (Chart 2). Strong base-promoted proton abstraction of the



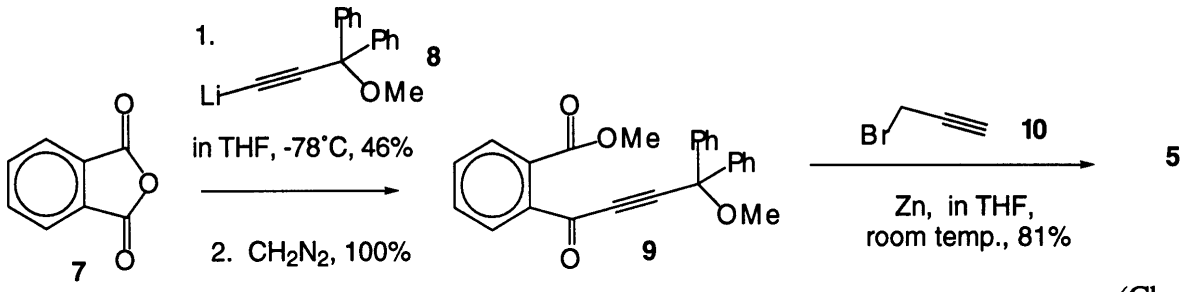
(Chart 2)

propargylic position and subsquent ring opening of lactone would give the enediyne **6**. The resulting carboxylic acid **6** was expected to be stable, because the triggering action (**1** → **3**) does not occur under these conditions.[2] It is noteworthy that this synthetic route enables us *not only* to prepare the

* To whom correspondence should be addressed.

cis-enediynes *but also* to produce carboxylic acid functionality as an intramolecular triggering device in one step.

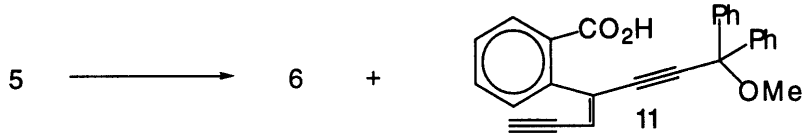
The key intermediate **5** was prepared starting from phthalic anhydride (**7**) in three steps (Chart 3). The lithiated alkyne **8**[4] was condensed with **7**, followed by methylation to give the acetylenic ketone **9** in 46% yield. Condensation of the ketone **9** with propargyl bromide (**10**) in the presence of zinc gave the desired lactone **5** in 81% yield.



(Chart 3)

We attempted the elimination reaction of **5** by employing various bases and solvents, as shown in Table 1.[5] Use of potassium hydroxide as a base did not give the desired product, probably because ordinary saponification to the hydroxy acid salt occurred, which was immediately converted to the starting lactone **5** after acidification (entry 1). The lactone **5** was inert against 4-dimethylaminopyridine (DMAP) (entries 2 and 3). When 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) was used as a base in tetrahydrofuran (THF), an approximately 1:1 mixture of the desired enediyne acid **6** and *trans*-olefin **11** was obtained (entry 4). To accelerate the push-pull reaction, weak acid (pyridinium *p*-toluenesulfonate (PPTS)) was added but *cis*-stereoselectivity was not improved (entries 5 and 6). Therefore, we surveyed the elimination reactions with DBU in various solvents (entries 7 - 12). Finally, the desired compound **6** was obtained in satisfactory yield with high *cis*-selectivity when the reaction was carried out in hexamethylphosphoric triamide (HMPA) (entry 12).

Table 1



Entry	Base	Solvent	Temp.	Yield of **6+11**	Ratio of **6:11**
1	KOH	MeOH	rt	0	-
2	DMAP	THF	66	0	-
3	DMAP	HMPA	80	0	-
4	DBU	THF	70	94	46:54
5	DBU [a)]	THF	70	92	42:58
6	DBU [b)]	THF	70	79	40:60
7	DBU	Benzene	70	77	31:69
8	DBU	CH_3CN	70	72	43:57
9	DBU	CH_3NO_2	100	0	-
10	DBU [c)]	-	50	78	57:43
11	DBU	DMSO	70	39	69:31
12	DBU	HMPA	70	63	**91:09**

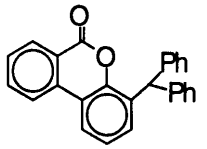
a) 2 eq to **5**. b) 3 eq to **5**. c) Used as a solvent.

The general procedure is as follows: a solution of **5** (195 mg, 0.497 mmol) and DBU (0.09 ml, 0.522 mmol) in HMPA (5 ml) was stirred at 60°C for 2 h. The resulting mixture was diluted with ether and poured into 5% aqueous $KHSO_4$. The resulting mixture was extracted with two portions of ether. The combined organic layers were washed with brine, dried over $MgSO_4$, and concentrated *in vacuo*. The residue was purified by column chromatography on silica gel eluted with hexane/ethyl acetate (4/1) to give **6**[6] and **11**[7] (91:9, checked by ^{1}H-NMR) in 63% isolated yield. The structure of carboxylic acids **6** and **11** was identified as their methyl esters **12** and **13**, respectively.[8]

Thus, we have developed a new synthetic method for an acyclic *cis*-enediyne system possessing carboxylic acid functionality in a one-step reaction. Now we are applying the new method to the molecular design and synthesis of various DNA-damaging enediynes.

REFERENCES AND NOTES

1) Myers A. G., Kuo E. Y., Finney, N. S., *J. Am. Chem. Soc.*, **111**, 8057-8059 (1989); Nagata R., Yamanaka H., Okazaki E., Saito I., *Tetrahedron Lett.*, **30**, 4995-4998 (1989).
2) Naoe Y., Kikuishi J., Ishigaki K., Iitsuka H., Nemoto H., Shibuya M., *Tetrahedron Lett.*, **36**, 9165-9168 (1995).
3) Shibuya M., Sakai Y., Naoe Y., *Tetrahedron Lett.*, **36**, 897-900 (1995).
4) The lithiated alkyne **8** was prepared from Me_3Si-C≡C-Li and acetophenone followed by treatment with Me_2SO_4 and K_2CO_3.
5) All the reactions shown in Table 1 except entries 1, 2, and 3 resulted in no recovery of the starting material **5**. Instead, unidentified molar materials were obtained.
6) Attempt of the Myers-Saito reaction of **6** under the same conditions[2] as for **1** (X=O) gave **14**.



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7) *cis*-Geometry for **6** and *trans*-geometry for **11** were determined by the comparison of the ^{1}H-NMR chemical shifts of olefinic protons reported in reference 2.
8) **12**: IR (neat) 3285, 2359, 2342, 1727, 1450, 1262, 1085, 763, 701 cm^{-1}: ^{1}H-NMR (JEOL FX200, 200MHz, $CDCl_3$).δ 7.80 (1H, dd, J = 1.7, 7.6 Hz, **H**-C=C-CO_2Me), 7.62 - 7.12 (13H, m, aromatics), 6.00 (1H, d, J = 2.4Hz, -C=C**H**-C≡C-H), 3.64 (s, 3H, -CO_2**Me**), 3.42 (1H, d, J = 2.4Hz, -C=CH-C≡C-**H**), 3.35 (3H, s, -C(C_6H_5)$_2$-O**CH$_3$**): ^{13}C-NMR (JEOL GX400, 100MHz, $CDCl_3$) δ 167.7, 143.1, 138.6, 136.0, 131.8, 130.4, 130.3, 129.5, 128.6, 128.1, 127.6, 126.9, 116.6, 96.7, 87.4, 85.0, 81.7, 81.5, 52.7, 52.2.
13: IR (neat) 3286, 2360, 2342, 1728, 1489, 1262, 1128, 1082, 772, 701 cm^{-1}: ^{1}H-NMR (JEOL FX200, 200MHz, $CDCl_3$).δ 7.94 (1H, d, J = 7.6 Hz, **H**-C=C-CO_2Me), 7.52 - 7.12 (13H, m, aromatics), 6.19 (1H, d, J = 2.4Hz, -C=C**H**-C≡C-H), 3.74 (s, 3H, -CO_2**Me**), 3.28 (1H, d, J = 2.4Hz, -C=CH-C≡C-**H**), 3.14 (3H, s, -C(C_6H_5)$_2$-O**CH$_3$**): ^{13}C-NMR (JEOL GX400, 100MHz, $CDCl_3$) δ.167.2, 143.0, 137.8, 135.7, 131.8, 130.5, 130.4, 130.0, 128.5, 128.1, 127.6, 126.7, 115.8, 93.2, 89.4, 86.2, 80.2, 81.3, 52.6, 52.2.

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