Secure route to the epoxybicyclo[7.3.0]dodecadienediyne core of the kedarcidin chromophore†

Kouki Ogawa,[a] Yasuhito Koyama,[a] Isao Ohashi,[a] Itaru Sato[b] and Masahiro Hirama*[ab]

Received (in Cambridge, UK) 21st August 2008, Accepted 23rd September 2008
First published as an Advance Article on the web 21st October 2008
DOI: 10.1039/b814595d

Formation of an epoxide before 9-membered ring cyclization and SmI_2 mediated reductive olefination in the presence of the epoxide successfully produced the epoxybicyclo[7.3.0]dodecadienediyne core of the kedarcidin chromophore.

The labile chromophore (**1**) of antiproliferative kedarcidin[1,2] has a highly functionalized epoxybicyclo[7.3.0]dodecadienediyne structure (Fig. 1).[3–5] In the course of our synthetic studies on the chromophore,[6,7] we found that the C8,9-epoxide was difficult to introduce at the later stages of the synthesis.[6a] Therefore, we envisaged that the formation of the epoxide functionality should be conducted before construction of the 9-membered ring framework. We recently developed the facile reductive elimination of vicinal bis-*p*-trifluoromethylbenzoates or 1,2-mesyloxy-*p*-trifluoromethylbenzoate using samarium iodide to introduce the olefins.[8] Kagan's pioneering work in the field of SmI_2 mediated reduction indicated that the epoxide functionality would serve as a good electron acceptor.[9,10] Indeed, reductive ring opening and deoxygenation reactions of epoxides in the presence or absence of proton sources proceeded under mild conditions.[9,11] In this communication we report a successful approach towards the epoxybicyclo[7.3.0]-dodecadienediyne core of the kedarcidin chromophore *via* the highly chemoselective reductive olefination of diol derivatives in the presence of an epoxide. To the best of our knowledge, this is the first example of a SmI_2 mediated reductive olefination of vicinal diol derivatives with the co-existence of an epoxide in the molecule.

Synthesis of the 9-membered epoxydiyne precursors for the crucial SmI_2 mediated reduction was initiated by the transformation of an enantioselectively prepared cyclopentene moiety **2**[6b] to an alkynyl epoxide structure (Scheme 1). Oxidation of diol **2** by SO_3·pyridine gave an α-hydroxyaldehyde. Addition of ethynyl Grignard reagent to the aldehyde in CH_2Cl_2–THF (10 : 1) proceeded diastereoselectively and the alkynyl alcohol **3** was obtained as a single diastereomer.[12] Selective mesylation of the newly formed secondary alcohol and subsequent treatment with DBU provided the desired *cis*-epoxide **4** after *C*-silylation of the alkyne terminus. The geometry of the C8,9-epoxide was unambiguously determined by the NOE correlation between H8 and H10. Hagihara–Sonogashira

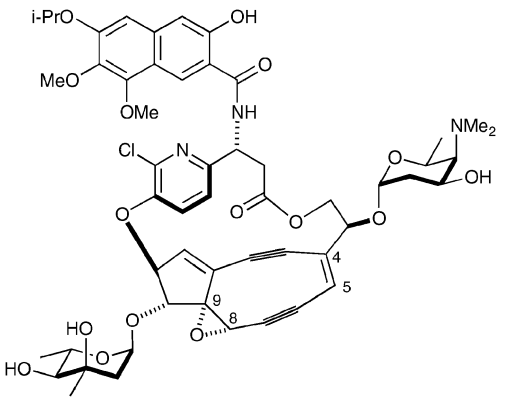


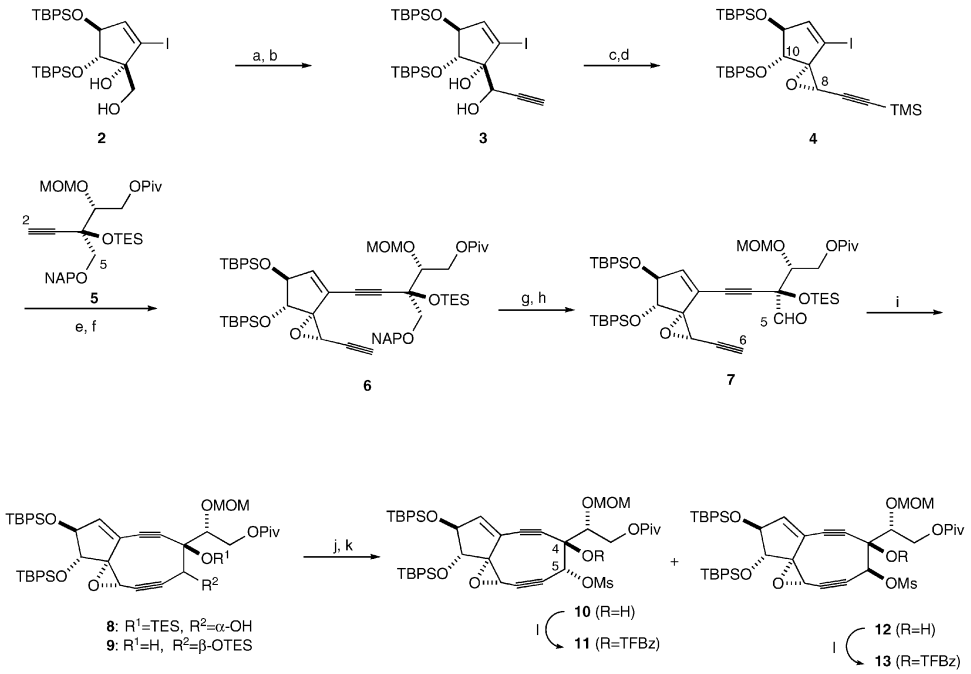
Fig. 1 The structure of the kedarcidin chromophore, **1**, proposed in 1997[3c] (recent stereochemical revision, see ref. 4).

coupling of **4** with the C2–C5 moiety **5**[13] and removal of the trimethylsilyl group afforded the terminal alkyne **6**. Oxidative cleavage of the 2-naphthylmethyl (NAP) ether and Dess–Martin oxidation gave the aldehyde **7**. Cyclization to the 9-membered diyne ring at the C5–C6 position utilizing $CeCl_3$–lithium disilazide at −25 °C[14] resulted in the formation of **8** and **9** (4 : 1). Selective cleavage of the triethylsilyl ethers using tetrabutylammonium fluoride at −78 °C and mesylation of the C5 alcohol allowed the separation of diastereomers **10** and **12**. The configuration at C5 was determined by comparison of the attempted epoxidation of diastereomers **10** and **12**. Only isomer **10** with the α-mesylate gave the corresponding C4,5-epoxide upon treatment with DBU. The C4 hydroxyl group in both isomers was acylated to give *p*-trifluoromethylbenzoates **11** and **13**. Diastereomers **11** and **13** were subjected to reductive elimination. The C5-acetoxy derivative **14**, instead of the mesylate, and *p*-trifluoromethyl benzoate **15** shown in Table 1 were also prepared from **8** and **9**, respectively.

Results of the reductive olefination[8,10,15] at the C4–C5 position are listed in Table 1. When α-mesylate **11** was treated with 2.5 molar equivalents of SmI_2 in THF at −15 °C, **11** disappeared within 6 min. Work up and rapid purification afforded enediyne **16** and its cycloaromatized product **17** in 60% combined yield (entry 1). Once the labile 9-membered enediyne **16** was formed, **16** underwent cycloaromatization and deterioration as in natural products.[2] The ratio of **16** and **17** after chromatographic purification was estimated to be *ca.* 3 : 2 by ^{1}H NMR spectroscopic analysis. It was less dependent on the reaction conditions than the period spent on work up and purification. The decomposition rate of **16** was also estimated ($t_{1/2}$ = 46 min at 24 °C in $CDCl_3$).[16] Excess use of SmI_2 (10 mol eq.) caused decomposition of substrate **11** even if the reaction was conducted at −78 °C. On the other hand,

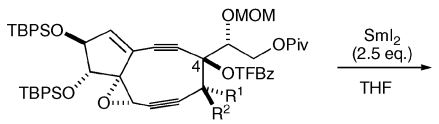
[a] *Department of Chemistry, Graduate School of Science, Tohoku University, Sendai 980-8578, Japan. E-mail: hirama@mail.tains.tohoku.ac.jp; Fax: +81-22-795-6566*
[b] *Research and Analytical Center for Giant Molecules, Graduate School of Science, Tohoku University, Japan. E-mail: isato@mail.tains.tohoku.ac.jp*

† Electronic supplementary information (ESI) available: Experimental details and characterisation data. See DOI: 10.1039/b814595d

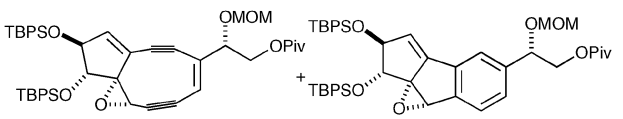


Scheme 1 *Reagents and conditions.* (a) SO_3·pyridine, Et_3N, DMSO, CH_2Cl_2; (b) ethynyl Grignard reagent, CH_2Cl_2, THF, 0 °C; (c) MsCl, Et_3N, CH_2Cl_2, −45 °C then DBU, 0 °C; (d) TMSCl, $LiN(TMS)_2$, THF, −30 °C, 44% (4 steps); (e) $Pd_2(dba)_3$·$CHCl_3$, CuI, *i*-Pr_2NEt, DMF; (f) K_2CO_3, MeOH, 72% (2 steps); (g) DDQ, H_2O, CH_2Cl_2; (h) Dess–Martin periodinane, $NaHCO_3$, CH_2Cl_2, 85% (2 steps); (i) $CeCl_3$, $LiN(TMS)_2$, THF, −20 °C, 58% (4 : 1); (j) Bu_4NF, THF, −78 °C; (k) Ms_2O, pyridine, CH_2Cl_2, 0 °C then separation; (l) *p*-$CF_3C_6H_4COCl$, DMAP, CH_2Cl_2, 59% (3 steps) for **11**, 19% (3 steps) for **13**. Abbreviations. TBPS: *tert*-butyldiphenylsilyl; TMS: trimethylsilyl; MOM: methoxymethyl; TES: triethylsilyl; NAP: 2-naphthylmethyl; TFBz: *p*-trifluoromethybenzoyl; DBU: 1,8-diazabicyclo[5.4.0]undec-7-ene; DDQ: 2,3-dichloro-5,6-dicyano-*p*-benzoquinone.

Table 1 Chemoselective reductive olefination mediated by SmI_2



11 R^1=OMs, R^2=H
13 R^1=H, R^2=OMs
14 R^1=OAc, R^2=H
15 R^1=H, R^2=OTFBz



Entry[a]	Substrate	R^1	R^2	Conditions	**16** + **17**[b] Yield (%)
1	**11**	OMs	H	−15 °C, 6 min	60
2	**13**	H	OMs	−20 °C, 10 min	72
3[c]	**13**	H	OMs	−20 °C, 10 min	59
4	**14**	OAc	H	0 °C, 17 min	53
5	**15**	H	OTFBz	−15 °C, 8 min	50

[a] For detailed reaction conditions, see ref. 17. [b] For the ratio of **16** and **17**, see text. [c] After the completion of the reaction, products were treated with excess 1,4-cyclohexadiene in CH_2Cl_2.

treatment of the β-mesylate **13** with 2.5 mol eq. of SmI_2 at −20 °C afforded a mixture of enediyne **16** and its aromatized product **17** in 72% yield (entry 2).[17] When the crude products were treated with excess 1,4-cyclohexadiene in CH_2Cl_2 (entry 3), cycloaromatized **17** was isolated as the sole product. Observed yields in the reductive elimination of **11** and **13** indicated that the relative configuration of the leaving group at C5 did not affect the efficiency of the elimination. The C5-acetate **14** and the C5-*p*-trifluoromethyl benzoate **15** were also found to act as substrates for the SmI_2 mediated reductive elimination (entries 4 and 5), but the reaction rate of **14** was slower as anticipated.

Thus, it is apparent that the electron transfer to the C8,9-epoxide is slower than that to the *p*-trifluoromethylbenzoate, which generates a tertiary radical at C4. The second electron transfer affords an anionic intermediate leading to the conjugate enediyne *via* elimination of mesylate.[8] The overall procedure corresponds to the highly chemoselective and facile reductive olefin formation from 1,2-diol derivatives under mild conditions.

In conclusion, we succeeded in the construction of the epoxybicyclo[7.3.0]dodecadienediyne framework of the kedarcidin chromophore *via* 9-membered ring cyclization at the C5–C6 position and subsequent SmI_2 mediated reductive olefination. The latter reduction shows unique chemoselectivity and the epoxide functionality survives under the reaction conditions. Further studies towards the total synthesis of the kedarcidin chromophore utilizing the present methodology are currently under investigation.

This work was supported financially by a Grant-in-Aid for Specially Promoted Research from the Ministry of Education, Culture, Sports, Science and Technology (MEXT) and SORST, Japan Science and Technology Agency (JST).

 This journal is © The Royal Society of Chemistry 2008

Notes and references

1 (*a*) K. S. Lam, G. A. Hesler, D. R. Gustavson, A. R. Crosswell, J. M. Veitch, S. Forenza and K. Tomita, *J. Antibiot*., 1991, **44**, 472; (*b*) S. J. Hofstead, J. A. Matson, A. R. Malacko and H. Marquardt, *J. Antibiot*., 1992, **45**, 1250.

2 (*a*) A. L. Smith and K. C. Nicolaou, *J. Med. Chem*., 1996, **39**, 2103; (*b*) Z. Xi and I. H. Goldberg, in *Comprehensive Natural Product Chemistry*, ed. D. H. R. Barton and K. Nakanishi, Pergamon, Oxford, 1999, vol. 7, p. 553; (*c*) M. Kar and A. Basak, *Chem. Rev*., 2007, **107**, 2861.

3 (*a*) J. E. Leet, D. R. Schroeder, S. J. Hofstead, J. Golik, K. L. Colson, S. Huang, S. E. Klohr, T. W. Doyle and J. A. Matson, *J. Am. Chem. Soc*., 1992, **114**, 7946; (*b*) J. E. Leet, D. R. Schroeder, D. R. Langley, K. L. Colson, S. Huang, S. E. Klohr, M. S. Lee, J. Golik, S. J. Hofstead, T. W. Doyle and J. A. Matson, *J. Am. Chem. Soc*., 1993, **115**, 8432; J. E. Leet, D. R. Schroeder, D. R. Langley, K. L. Colson, S. Huang, S. E. Klohr, M. S. Lee, J. Golik, S. J. Hofstead, T. W. Doyle and J. A. Matson, *J. Am. Chem. Soc*., 1994, **116**, 2233; Structure revision: (*c*) S. Kawata, S. Ashizawa and M. Hirama, *J. Am. Chem. Soc*., 1997, **119**, 12012.

4 Recent stereochemical revision: F. Ren, P. C. Hogan, A. J. Anderson and A. G. Myers, *J. Am. Chem. Soc*., 2007, **129**, 5381.

5 For the chromophores of related chromoprotein antibiotics, C-1027: (*a*) K. Yoshida, Y. Minami, R. Azuma, M. Saeki and T. Otani, *Tetrahedron Lett*., 1993, **34**, 2637; (*b*) K. Iida, T. Ishii, M. Hirama, T. Otani, Y. Minami and K. Yoshida, *Tetrahedron Lett*., 1993, **34**, 4079; (*c*) K. Iida, S. Fukuda, T. Tanaka, M. Hirama, S. Imajo, M. Ishiguro, K. Yoshida and T. Otani, *Tetrahedron Lett*., 1996, **38**, 4997; Maduropeptin: (*d*) D. R. Schroeder, K. L. Colson, S. E. Klohr, N. Zein, D. R. Langley, M. S. Lee, J. A. Matson and T. W. Doyle, *J. Am. Chem. Soc*., 1994, **116**, 9351; (*e*) N. Zein, W. Solomon, K. L. Colson and D. R. Schroeder, *Biochemistry*, 1995, **34**, 11591.

6 (*a*) F. Yoshimura, M. J. Lear, I. Ohashi, Y. Koyama and M. Hirama, *Chem. Commun*., 2007, 3057; (*b*) Y. Koyama, M. J. Lear, F. Yoshimura, I. Ohashi, T. Mashimo and M. Hirama, *Org. Lett*., 2005, **7**, 267; (*c*) M. J. Lear, F. Yoshimura and M. Hirama, *Angew. Chem., Int. Ed*., 2001, **40**, 946; (*d*) F. Yoshimura, S. Kawata and M. Hirama, *Tetrahedron Lett*., 1999, **40**, 8281; (*e*) S. Kawata and M. Hirama, *Tetrahedron Lett*., 1998, **39**, 8707.

7 Synthetic studies conducted by other groups. See also ref. 4. (*a*) A. G. Myers, P. C. Hogan, A. R. Hurd and S. D. Goldberg, *Angew. Chem., Int. Ed*., 2002, **41**, 1062; (*b*) A. G. Myers and S. D. Goldberg, *Angew. Chem., Int. Ed*., 2000, **39**, 2732; (*c*) S. Caddick, V. M. Delisser, V. E. Doyle, S. Khan, A. G. Avent and S. Vile, *Tetrahedron*, 1999, **55**, 2737; (*d*) P. Magnus, R. Carter, M. Davies, J. Elliot and T. Pitterna, *Tetrahedron*, 1996, **52**, 6283; (*e*) T. Takahashi, H. Tanaka, H. Yamada, T. Matsumoto and Y. Sugiura, *Angew. Chem., Int. Ed. Engl*., 1996, **35**, 1835; (*f*) O. Gebauer and R. Brückner, *Synthesis*, 2000, 588.

8 (*a*) M. Inoue, I. Ohashi, T. Kawaguchi and M. Hirama, *Angew. Chem., Int. Ed*., 2008, **47**, 1777; (*b*) K. Komano, S. Shimamura, M. Inoue and M. Hirama, *J. Am. Chem. Soc*., 2007, **129**, 14184.

9 (*a*) P. Girard, J. L. Namy and H. B. Kagan, *J. Am. Chem. Soc*., 1980, **102**, 2693; (*b*) J. L. Namy, P. Girard, H. B. Kagan and P. E. Caro, *Nouv. J. Chim*., 1981, **5**, 479.

10 Reviews: (*a*) J. M. Concellón and H. Rodríguez-Solla, *Chem. Soc. Rev*., 2004, **33**, 599; (*b*) H. B. Kagan, *Tetrahedron Lett*., 2003, **59**, 10351; (*c*) P. G. Steel, *J. Chem. Soc., Perkin Trans. 1*, 2001, 2727; (*d*) A. Gansäuer and H. Bluhm, *Chem. Rev*., 2000, **100**, 2771; (*e*) G. A. Molander, *Chem. Rev*., 1992, **92**, 29.

11 (*a*) M. Matsukawa, T. Tabuchi, J. Inanaga and M. Yamaguchi, *Chem. Lett*., 1987, 2101; (*b*) E. J. Corey and G. Z. Zheng, *Tetrahedron Lett*., 1997, **38**, 2045; (*c*) A. Gansäuer and B. Rinker, *Tetrahedron*, 2002, **58**, 7017; (*d*) M. Inoue, S. Hatano, M. Kodama, T. Sasaki, T. Kikuchi and M. Hirama, *Org. Lett*., 2004, **6**, 3833.

12 M. Inoue, T. Sasaki, M. Hatano and M. Hirama, *Angew. Chem., Int. Ed*., 2004, **43**, 6500.

13 Synthesized in eleven steps from an adequately protected L-threitol derivative (A. Ishiwata, S. Sakamoto, T. Noda and M. Hirama, *Synlett*, 1999, 692). Also see ESI†.

14 (*a*) K. Iida and M. Hirama, *J. Am. Chem. Soc*., 1994, **116**, 10310; (*b*) I. Sato, K. Toyama, T. Kikuchi and M. Hirama, *Synlett*, 1998, 1308; Also see: (*c*) A. G. Myers, P. M. Harrington and E. Y. Kuo, *J. Am. Chem. Soc*., 1991, **113**, 694; (*d*) T. Nishikawa, M. Isobe and T. Goto, *Synlett*, 1991, 393.

15 For recent examples of related reactions, see: (*a*) J. M. Concellón, H. Rodríguez-Solla, C. Simal and M. Huerta, *Org. Lett*., 2005, **7**, 5833; (*b*) V. Reutrakul, S. Jarussophon, M. Pohmakotr, Y. Chaiyasut, S. U-Thet and P. Tuchinda, *Tetrahedron Lett*., 2002, **43**, 2285; (*c*) A. S. Kende and J. S. Mendoza, *Tetrahedron Lett*., 1990, **31**, 7105; (*d*) M. Ihara, S. Suzuki, T. Taniguchi, Y. Tokunaga and K. Fukumoto, *Tetrahedron*, 1995, **51**, 9873; (*e*) I. E. Markó, F. Murphy, L. Kumps, A. Ates, R. Touillaux, D. Craig, S. Carballares and S. Dolan, *Tetrahedron*, 2001, **57**, 2609; (*f*) K. Shibuya and M. Shiratsuchi, *Synth. Commun*., 1995, **25**, 431.

16 For the structure and reactivity of 9-membered enediynes, see: (*a*) K. Iida and M. Hirama, *J. Am. Chem. Soc*., 1995, **117**, 8875; (*b*) M. Hirama, *Pure Appl. Chem*., 1997, **69**, 525; (*c*) T. Usuki, T. Mita, M. J. Lear, P. Das, F. Yoshimura, M. Inoue, M. Hirama, K. Akiyama and S. Tero-Kubota, *Angew. Chem., Int. Ed*., 2004, **43**, 5249; (*d*) M. Hirama, K. Akiyama, P. Das, T. Mita, M. J. Lear, K. Iida, I. Sato, F. Yoshimura, T. Usuki and S. Tero-Kubota, *Heterocycles*, 2006, **69**, 83, and references therein; (*e*) A. G. Myers, A. R. Hurd and P. C. Hogan, *J. Am. Chem. Soc*., 2002, **124**, 4583.

17 Typical experimental procedure for SmI_2 mediated reductive olefination. A 0.1 M THF solution of SmI_2 was prepared from samarium and diiodomethane according to the procedure reported by Kagan (ref. 9*b*). To a solution of **13** (4.2 mg, 3.7 μmol) in freshly distilled THF (0.64 mL) was added a solution of SmI_2 (0.1 M, 90 μl, 9.1 μmol) at −20 °C. After stirring for 10 min, the mixture was exposed to open air and diluted with diethyl ether. The suspension was filtrated through pads of Celite and silica gel. Concentration under reduced pressure and silica gel flash chromatography (hexane–ethyl acetate) gave a mixture of enediyne **16** and aromatized product **17** in a ratio of 3 : 2 (2.3 mg, 72% as a combined yield).