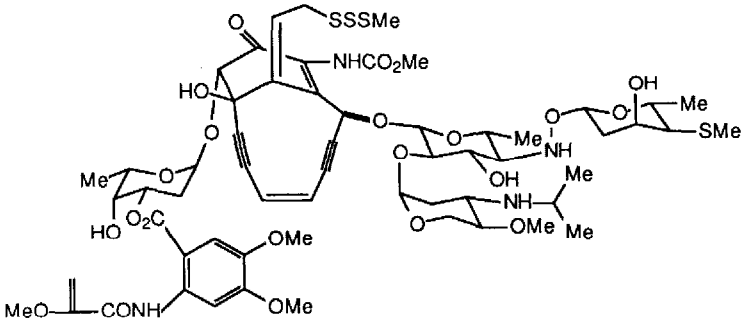
Tetrahedron Letters, Vol.30, No.7, pp 851-854, 1989 0040-4039/89 $3.00 + .00
Printed in Great Britain Pergamon Press plc

SYNTHESIS OF THE CORE ENEDIYNE STRUCTURE OF ESPERAMICIN-CALICHEMICIN CLASS OF ANTITUMOR ANTIBIOTICS

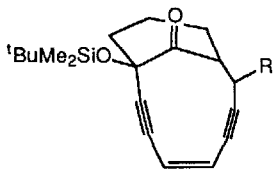
Kiyoshi Tomioka,* Hitoshi Fujita,[1] and Kenji Koga
Faculty of Pharmaceutical Sciences, University of Tokyo,
Hongo, Bunkyo-ku, Tokyo 113, Japan

Summary: The core structure of esperamicin-calichemicin series, bicyclo[7.3.1]enediyne 2, was synthesized in 9% overall yield in eight steps from cyclohexane-1,2-dione and was shown to be stable at room temperature.

The heart of esperamicin-calichemicin class of novel antitumor antibiotics (e.g., **1**) is a bicyclo[7.3.1]tridecane system that combines a methyl trisulfide group, an endocyclic α,β-unsaturated ketone, and double and triple bonds in a 3-ene-1,5-diyne relationships.[2-4] Enzymatic reduction of a trisulfide to a thiol triggers intramolecular Michael addition of the thiol to the enone, and subsequent Bergman enediyne cyclization to a phenylene diradical which can abstract protons from deoxyribose units in deoxyribonucleic acid resulting DNA strand breakage. Inspired by these fascinating structures, much efforts have been devoted toward design, synthesis, and evaluation of simple structures that might mimic the biological action of natural products.[5]



1 Esperamicin A_1



2 R = H
3 R = O-sugar

As a part of our continuing program aimed at the asymmetric total synthesis of antitumor natural products,[6] we have also engaged in this attractive and challenging field and our initial goal for the synthetic studies is bicyclo[7.3.1]enediynes **2**, **3** which are expected to be stable at the ambient temperature toward Bergman cyclization due to the presence of carbonyl group at the bridging chain. Quite recently the synthesis of compound **2** has been reported by Magnus and his co-workers.[5b,f] In the present communication, we report an independent synthesis of a bicyclo[7.3.1]tridecane **2** which contains an enediyne unit in a requisite linear arrangement.

Our synthesis of **2** began with the reaction of cyclohexane-1,2-dione **4** with acetylene.[7] Treatment of **4** with ethynylmagnesium bromide in THF at room temperature for 0.5 h afforded **5** as colorless needles (mp 50-51 °C) in 76% yield.[8] Protection of **5** with *t*-butyldimethylsilyl group (*t*-$BuMe_2SiOTf$/2,6-lutidine/CH_2Cl_2, 0 °C, 1.5 h) provided **6** as colorless plates (mp 38-40 °C) in 98%

yield. Stephans-Castro coupling reaction[9] of **6** with Z-dichloroethene ($Pd(PPh_3)_4$/CuI/*i*-Pr_2NH/benzene, rt, 1 h) provided **7** as a colorless oil in 79% yield. Further coupling reaction of **7** with methyl propargyl ether ($Pd(PPh_3)_4$/CuI/$BuNH_2$/benzene, rt, 12 h) afforded **8** as a colorless oil in 53% yield. Me_3Si-enol ether **9** and *t*-$BuMe_2Si$-enol ether **10** were prepared from **8** by treating with Me_3SiOTf and *t*-$BuMe_2SiOTf$ in refluxing Et_3N in 86 and 88% yields, respectively.[10]

Treatment of Me_3Si-enol ether **9** and *t*-$BuMe_2Si$-enol ether **10** with $Co_2(CO)_8$ in *n*-heptane at room temperature for 2 h provided the corresponding dicobalt hexacarbonyl adducts, **11** and **12**,[11,12] in 68 and 88% yields, respectively.

Cyclization of **11** and **12** was carried out under the standard Nicholas conditions.[11,12] Thus, treatment of Me_3Si-enol ether **11** with $TiCl_4$ (3.0 equiv)/DABCO (1.0 equiv) in CH_2Cl_2 at -60 °C for 10 min smoothly provided **13** as a brown solid in 64% yield. On the other hand, treatment of *t*-$BuMe_2Si$-enol ether **12** afforded **14** as a major product, probably arising from hydroxylation of the corresponding allylic carbocation species generated by desilyloxylation.[13] We believe that trimethylsilyl group facilitates the attack of enol-double bond to terminal carbocation species, due to the less bulkiness of the group than *t*-butyldimethylsilyl group.

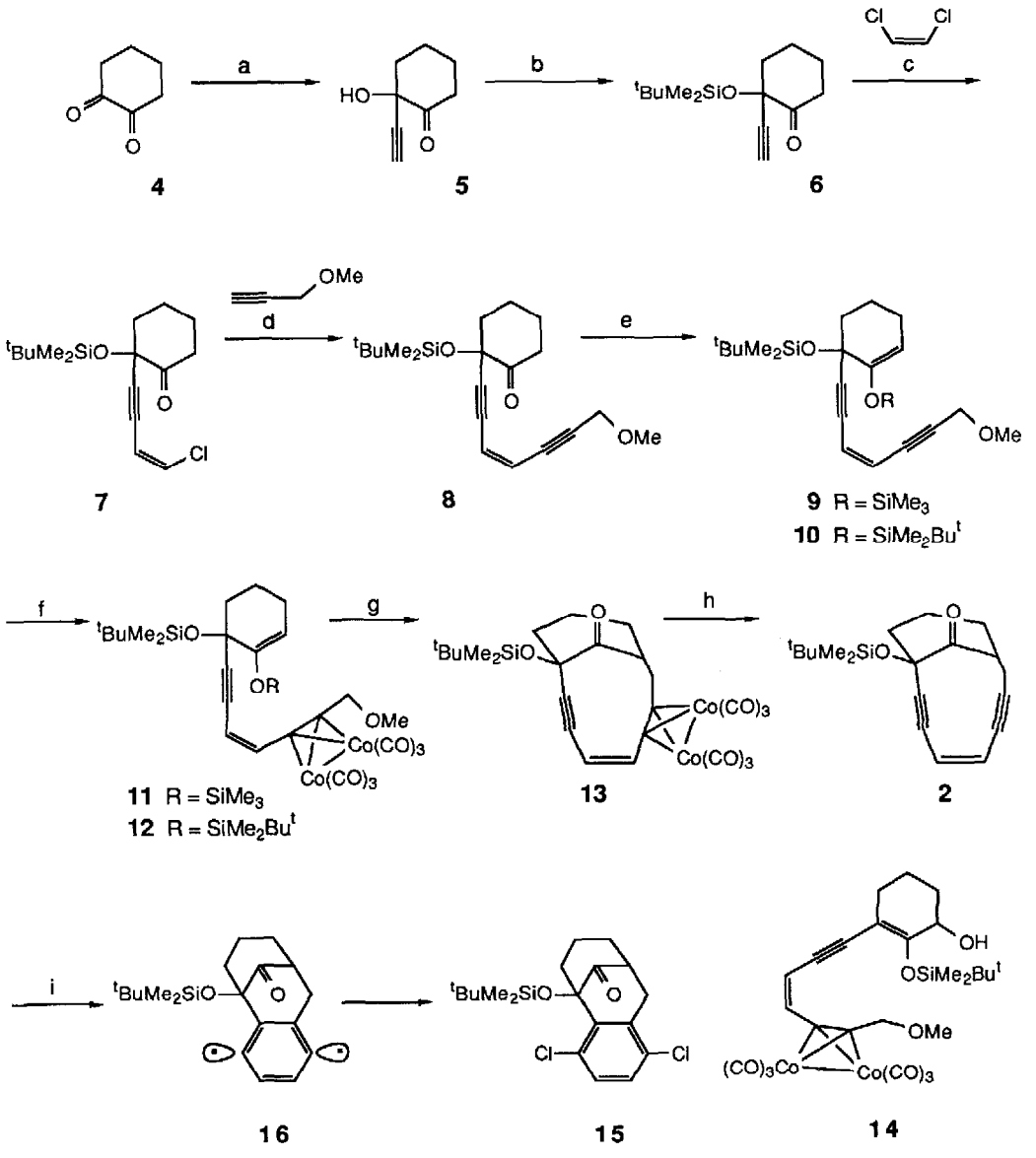
Decomplexation of **13** with Me_3NO (10 equiv) in MeOH at room temperature for 12 h provided the desired bicyclo[7.3.1]enediyne **2** as colorless needles (dp 42-45 °C) in 73% yield without formation of any detectable amount of Bergman reaction product.[14]

Bergman cyclization of **2** took place by heating at reflux for 4 h in CCl_4 to afford dichloride **15** in 30% yield, indicating involvement of a phenylene diradical intermediate **16** in the reaction. Evaluation of biological activity of **2** is in progress and will be reported elsewhere.

Further studies toward the synthesis of esperamicin-calichemicin aglycone are in progress in our laboratories.

References and Notes

1. Visiting scientist from Sumitomo Pharmaceutical Co., Osaka, Japan.
2. Isolation: Esperamicin: J. Golic, J. Clardy, G. Dubay, G. Groenewold, H. Kawaguchi, M. Konishi, B. Krishnan, H. Ohkuma, K. Saitoh, and T. W. Doyle, *J. Am. Chem. Soc.*, **109**, 3461 (1987); J. Golic, G. Dubay, G. Groenewold, H. Kawaguchi, M. Konishi, B. Krishnan, H. Ohkuma, K. Saitoh, and T. W. Doyle, *Ibid*, **109**, 3462 (1987).
   Calichemicin: M. D. Lee, T. S. Dunne, M. M. Siegel, C. C. Chang, G. O. Morton, and D. B. Borders, *J. Am. Chem. Soc.*, **109**, 3646 (1987); M. D. Lee, T. S. Dunne, C. C. Chang, G. A. Ellestad, M. M. Siegel, G. O. Morton, W. J. McGahren, and D. B. Borders, *Ibid*, **109**, 3646 (1987).
3. Interaction with DNA: N. Zein, A. M. Sinha, W. J. McGahren, and G. A. Ellestad, *Science*, **240**, 1198 (1988); K. C. Nicolaou, Y. Ogawa, G. Zuccarello, and H. Kataoka, *J. Am. Chem. Soc.*, **110**, 7247 (1988).
4. Neocarzinostatin has also been proposed to generate a diradical species for biological action. K. Edo, M. Mizugaki, Y. Koide, H. Seto, K. Furihata, N. Otake, and N. Ishida, *Tetrahedron Lett.*, **26**, 331 (1985); A. G. Myers, *Ibid.*, **28**, 4493 (1987); P. A. Wender, M. Harmata, D. Jeffrey, C. Mukai, and J. Suffert, *Ibid.*, **29**, 909 (1988).



a) HC≡CMgBr/THF, rt, 0.5 h, 76%; b) $^{t}BuMe_2SiOTf$/2,6-lutidine/CH_2Cl_2, 0 °C, 1.5 h, 98%; c) *Z*-dichloroethene/$Pd(PPh_3)_4$/CuI/*i*-Pr_2NH/benzene, rt, 1 h, 79%; d) methyl propargyl ether/ $Pd(PPh_3)_4$/CuI/$BuNH_2$/benzene, rt, 12 h, 53%; e) Me_3SiOTf/Et_3N, reflux, 1 h, 86% for **9** ($^{t}BuMe_2SiOTf/Et_3N$, reflux, 2.5 h, 88% for **10**); f) $Co_2(CO)_8$/*n*-heptane, rt, 2 h, 68% for **11** (88% for **12**); g) **11**-$TiCl_4$ (3.0 equiv)/DABCO (1.0 equiv)/CH_2Cl_2, -60 °C, 10 min, 64%; h) Me_3NO/MeOH, rt, 12 h, 73% i) reflux in CCl_4, 4 h, 30%

5. Synthetic studies: a) S. L. Schreiber and L. L. Kiessling, *J. Am. Chem. Soc.*, **110**, 631 (1988); b) P. Magnus and P. A. Carter, *Ibid.*, **110**, 1626 (1988); c) K. C. Nicolaou, G. Zuccarello, Y. Ogawa, E. J. Schweiger, and T. Kumazawa, *Ibid.*, **110**, 4866 (1988); d) S. J. Danishefsky, N. B. Mantlo, and D. S. Yamashita, *Ibid.*, **110**, 6890 (1988); e) A. S. Kende and C. A. Smith, *Tetrahedron Lett.*, **29**, 4217 (1988); f) P. Magnus, R. T. Lewis, and J. C. Huffman, *J. Am. Chem. Soc.*, **110**, 6921 (1988).
6. For example, K. Tomioka, A. Hagiwara, and K. Koga, *Tetrahedron Lett.*, **29**, 3095 (1988).
7. G. M. Pilling and F. Sondheimer, *J. Am. Chem. Soc.*, **93**, 1970 (1971).
8. Satisfactory spectroscopic and analytical data were obtained for all new compounds described in the present communication. Yields referred to the purified compounds by silica gel column chromatography.
9. R. D. Stephans and C. E. Castro, *J. Org. Chem.*, **28**, 3313 (1963); D. Guillerm and G. Linstrumelle, *Tetrahedron Lett.*, **27**, 5857 (1986); A. S. Kende and C. A. Smith, *J. Org. Chem.*, **53**, 2655 (1988).
10. Selected 100 MHz ^{13}C-NMR ($CDCl_3$) δ: **9** -3.22 (q), -3.01(q), 0.40 (q), 18.24 (s), 18.97 (t), 24.17 (t), 25.86 (q), 41.04 (t), 57.59 (q), 60.45 (t), 69.62 (s), 81.23 (s), 83.89 (s), 92.12 (s), 101.08 (s), 104.59 (d), 118.19 (d), 119.91 (d), 150.47(s); **10** -4.47 (q), -4.41 (q), -3.13 (q), -2.92 (q), 18.30 (s), 18.62 (t), 24.17 (t), 25.83 (q), 40.86 (t), 57.59 (q), 60.45 (t), 69.79 (s), 81.26 (s), 83.89 (s), 92.06 (s), 101.14 (s), 104.50 (d), 118.10 (d), 119.88 (d), 150.50 (s); **11** -3.25 (q), -3.16 (q), 0.38 (q), 18.10 (s), 18.62 (t), 24.19 (t), 25.83 (q), 40.45 (t), 58.64 (q), 69.82 (s), 73.18 (t), 81.76 (s), 82.23 (s), 94.91 (s), 103.53 (s), 104.47 (d), 110.60 (d), 135.67 (d), 150.01 (s), 199 (bs); **12** -4.65 (q), -4.24 (q), -3.19 (q), -3.04 (q), 18.27 (t), 24.17 (t), 25.86 (q), 40.10 (t), 58.70 (q), 70.02 (s), 73.35 (t), 81.73 (s), 82.43 (s), 94.66 (s), 103.48 (s), 104.73 (d), 110.63 (d), 135.67 (d), 150.09 (s), 199.34 (bs); **13** -3.25 (q), -2.84 (q), 18.18 (s), 18.79 (t), 25.65 (q), 32.60 (t), 39.61 (t), 42.47 (t), 49.82 (d), 75.66 (s), 82.40 (s), 92.62 (s), 95.10 (s), 97.14 (s), 109.72 (d), 142.45 (d), 199.60 (bs), 202.49 (s); **14** -4.15 (q), -3.89 (q), 18.30 (t), 25.71 (q), 28.78 (t), 31.26 (t), 58.84 (q), 67.75 (d), 73.47 (t), 82.61 (s), 91.62 (s), 94.63 (s), 99.42 (s), 102.86 (s), 111.88 (d), 135.53 (d), 155.84 (s), 199.31 (bs); **2** -3.16 (q), -3.10 (q), 18.36 (s), 18.77 (t), 24.19 (t), 24.49 (t), 25.86 (q), 25.92 (q), 36.83 (t), 48.34 (d), 74.31 (s), 83.45 (s), 91.54 (s), 97.49 (s), 100.24 (s), 121.34 (d), 124.46 (d), 204.30 (s).
11. K. M. Nicholas, *Acc. Chem. Res.*, **20**, 207 (1987).
12. S. L. Schreiber, T. Sammakia, and E. Crowe, *J. Am. Chem. Soc.*, **108**, 3128 (1986).
13. It is important to note that Magnus[5f] reported a successful Nicholas reaction of *t*-BuMe$_2$Si-enol ether **12** providing **13** as a major product. In our carefully controlled reaction, formation of only a trace amount of **13** was observed.
    In a model reaction with use of Me$_3$Si-enol ether and *t*-BuMe$_2$Si-enol ether of cyclohexanone, Me$_3$Si-enol ether provided alkylation product (dicobalt hexacarbonyl adduct of methyl propargyl ether/$TiCl_4$/DABCO/CH_2Cl_2) in 73% yield, whereas *t*-BuMe$_2$Si-enol ether did not provided isolable amount of alkylation product.
14. R. G. Bergman, *Acc. Chem. Res.*, **6**, 26 (1973); N. Darby, C. U. Kim, J. A. Salaün, K. W. Shelton, S. Takada, and S. Masamune, *J. Chem. Soc., Chem. Commun.*, **1971**, 1516.

(Received in Japan 14 November 1988)