Pergamon

Tetrahedron Letters, Vol. 38, No. 42, pp. 7353-7356, 1997

0040-4039/97 $17.00 + 0.00

PII: S0040-4039(97)10010-7

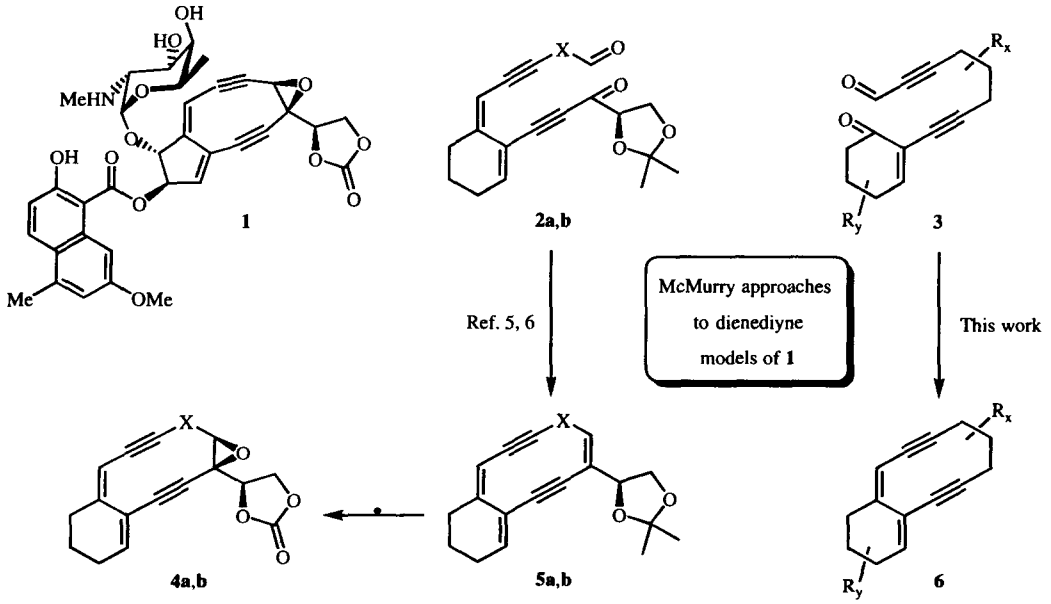
FIRST GENERATION OF THE DIENEDIYNE PORTION OF A DIENEDIYNE MODEL OF THE NEOCARZINOSTATIN CHROMOPHORE BY A MCMURRY REACTION

Mark Rucker and Reinhard Brückner*

Institut für Organische Chemie der Georg-August-Universität, Tammannstr. 2, D-37077 Göttingen, Germany

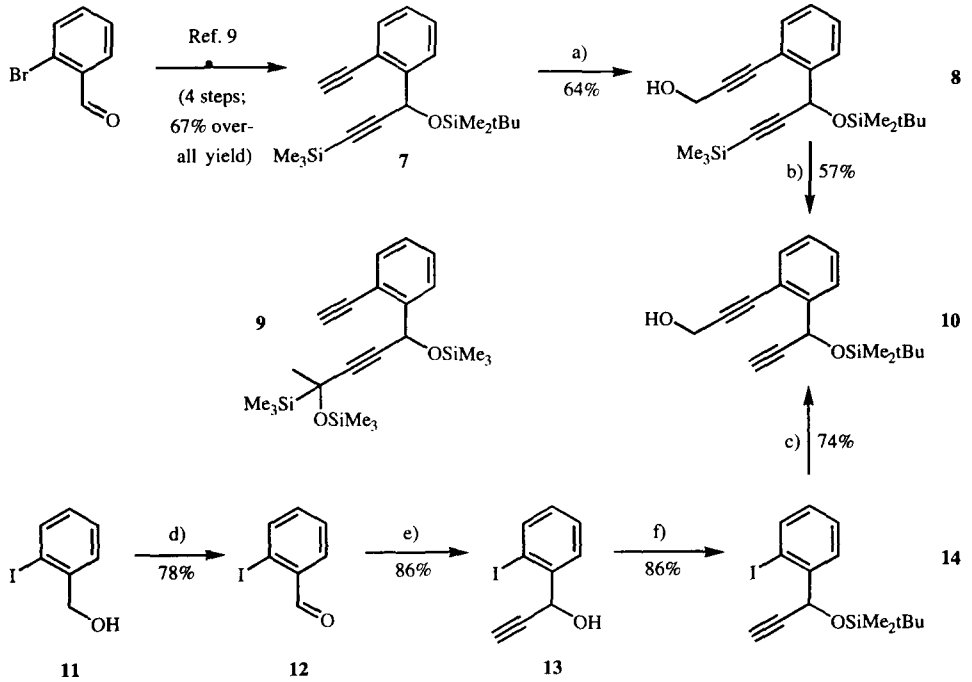
Abstract: The first **3**→**6** type ring-closing dienediyne synthesis by means of a McMurry reaction was realized by converting the ketoaldehyde **20** into the 6-/10-membered bicyclic dienediyne **22**. Diastereoselective pinacol couplings **20**→**23** and **21**→**24** giving 6-/10-membered bicyclic enediynediols were possible, too.
© 1997 Elsevier Science Ltd.

The neocarzinostatin chromophore **1** continues to arouse the interest of the organic chemical community because of its pronounced anti-tumor activity [1]. After the mechanism of action of compound **1** had been clarified [2], an intensive search for dienediynes started that would hopefully be stabler than the exceedingly labile natural product **1**. Many strategies were developed in this context [3]. Our own contribution is a bis(enol-trifluoromethanesulfonate) + alkyne$_1$ + alkyne$_2$ → dienediyne coupling approach [4]. It enabled us recently to synthesize the dienediyne epoxycarbonates **4a** [5] and **4b** [6], ring-expanded analogs with considerable structural resemblance to **1** [7]. Key-steps in these syntheses were McMurry couplings of the ketoaldehydes **2a** [5] and **2b** [6] which led to the trienediynes **5a** and **5b**, respectively (Scheme 1). The efficiency of these reactions suggested to ring-close under McMurry reactions also ketoaldehydes **3**. The first synthesis of a dienediyne **6** by such a strategy is communicated here [8].



Scheme 1.

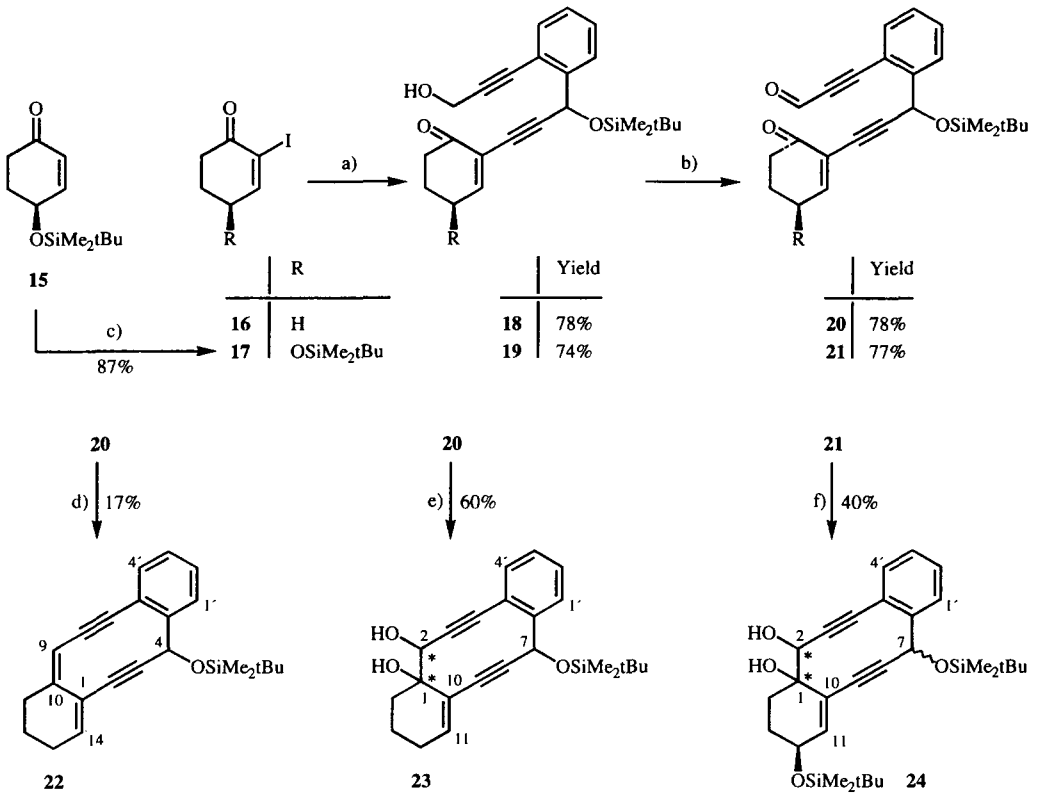
The diyne moiety of our type-**3** ketoaldehydes **20** and **21** was made accessible in form of building block **10** (Scheme 2). A first route to **10** proceeded via the diyne **7** [9] and was terminated by a hydroxymethylation of its ≡C-H group (→ propargyl alcohol **8**) and C-desilylation. A shorter and higher-yielding access to **10** was patterned subsequently – and at the time unknowingly – in analogy to Cunico's and Nair's recent synthesis of the related diyne **9** [10]. The commercially available iodobenzyl alcohol **11** was oxidized to aldehyde **12**. The latter reacted with ethynylmagnesium bromide to the propargyl alcohol **13**. Silylation with *tert*-butyldimethylsilyl chloride and a Pd-catalyzed coupling with 2-propyn-1-ol [11] furnished the diyne **10**. Its overall yield was 43% instead of the previously obtained 24%.



Scheme 2. *a) nBuLi (1.05 equiv.), THF, -78°C, 30 min; formaldehyde (4.0 equiv.), 3 h; 64%.– b) KF (2.0 equiv.), MeOH, room temp.; 4 h.– c) $Pd(PPh_3)_2Cl_2$ (0.05 equiv.), CuI (0.15 equiv.), propargyl alcohol (2.0 equiv.), $HN(iPr)_2$, THF, room. temp, 24 h.– d) PDC (1.5 equiv.), CH_2Cl_2, r.t., 12 h.– e) HC≡CMgBr (≤ 4.8 equiv.), THF, -60°C, 14 h.–f) tert-$BuMe_2SiCl$ (3.3 equiv.), imidazole (3.0 equiv.), CH_2Cl_2, room. temp., 12 h.*

Diyne **10** was coupled with the iodocyclohexenone **16** in the presence of $Pd_2(dba)_3$•$CHCl_3$ and P(2-furyl)$_3$ at room temperature in 78% yield (→**18**; Scheme 3). A similar coupling (→ 74% **19**) succeeded between diyne **10** and the iodocyclohexenone **17** which stemmed from the iodination [12] of Danishefsky's enantiopure cyclohexenone **15** [13]. The coupling products **18** and **19** were oxidized with the Dess-Martin reagent [14] to the ketoaldehydes **20** and **21**, respectively. These compounds were treated with low-valent titanium [15] under the conditions of the previously realized **2a**→**5b** [5] and **2b**→**5b** conversions [6]. *At +30°C, the mono-siloxylated ketoaldehyde **20** underwent the desired olefination reaction and delivered the benz-annulated dienediyne **22** in 17% yield.* Two olefinic 300 MHz ^{1}H NMR resonances δ = 5.87 (9-H) and 6.09 (14-H) and corresponding 126 MHz ^{13}C NMR lines at δ = 106.37 (C-9) and 140.09 (C-14) underscore the correctness of our structure assignment [16].

A similar dienediyne synthesis starting from the bis-siloxylated dicarbonyl compound **21** failed. However, *pinacol couplings* succeeded with the mono- (**20**) *and* with the bis-siloxylated ketoaldehyde (**20**) upon treatment with low-valent titanium at -20°C [15]. Remarkably, both pinacol couplings **20**→**23** [17] and **21**→**24** were completely diastereoselective. This propensity along with the higher yields of these reactions (60% and 40%, respectively) compared to the 17%-yielding McMurry reaction **20**→**22** make it worthwhile in the future trying to derive type-**6** dienediynes from type-**3** ketoaldehydes via pinacol intermediates rather than directly.



Scheme 3. *a)* ***10****, $Pd_2dba_3CHCl_3$ (0.04 equiv.), tris(2-furyl)phosphine (0.12 equiv.), CuI (0.12 equiv.), NEt_3, THF, room temp., 1 h.– b) Dess-Martin periodinane (1.3 equiv.), CH_2Cl_2, room temp., 1.5 h.– c) I_2 (4.2 equiv.), pyridine/CH_2Cl_2 (v/v; 1:1), 0°C, 2 h.– d) DME complex of pre-reduced [by refluxing with Zn/Cu couple (183 equiv.) in DME for 6 h] $TiCl_3$ (62 equiv.); addition of DME solution of* **20** *by syringe pump at 30°C during 4 h.– e) DME complex of pre-reduced [by refluxing with Zn, Cu couple (92 equiv.) in DME for 6 h] $TiCl_3$ (30 equiv.); addition of DME solution of* **20** *by syringe pump at -20°C during 4 h.– f) Same es (e) with solution of* **21***.– * Only one configuration realized at this stereocenter relative to other stereocenter(s) of this compound.*

REFERENCES AND NOTES

1. Structure: Shibuya, M.; Toyooka, K.; Kubota, S. *Tetrahedron Lett.* **1984**, *25*, 1171-1174; Edo, K.; Mizugaki, M.; Koide, Y.; Seto, H.; Furihata, K.; Otake, N.; Ishida, N. *Tetrahedron Lett.* **1985**, *26*, 331-334; Edo, K.; Akiyama, Y.; Saito, K.; Mizugaki, M. *J. Antibiot.* **1986**, *39*, 1615-1619; Myers, A. G.; Proteau, P. J.; Handel, T. M. *J. Am. Chem. Soc.* **1988**, *110*, 7212-7214. Chemistry: Goldberg; I. H. *Acc. Chem. Res.* **1991**, *24*, 191-198; Hirama, M. *J. Synth. Org. Chem. Jpn.* **1994**, *52*, 980-991.
2. Myers, A. G.; Proteau, P. J. *J. Am. Chem. Soc.* **1989**, *111*, 1146-1147; Myers, A. G.; Cohen, S. B.; Kwon, B.-M. *J. Am. Chem. Soc.* **1994**, *116*, 1670-1682.
3. Lhermitte, H.; Grierson, D. *Contemp. Org. Synth.* **1996**, *3*, 93-124; Grissom, J. W.; Gunawardena, G. U.; Klingberg, D.; Huang, D. *Tetrahedron* **1996**, *52*, 6453-6518; Suffert, J.; Brückner, R. *Lettre des Sciences Chimiques*, février-avril **1996**, 25-29.
4. Brückner, R.; Scheuplein, S. W.; Suffert, J. *Tetrahedron Lett.* **1991**, *32*, 1449-1452; Scheuplein, S. W.; Harms, K.; Brückner, R.; Suffert, J. *Chem. Ber.* **1992**, *125*, 271-278; Moniatte, M.; Eckhardt, M.; Brickmann, K.; Brückner, R.; Suffert, J. *Tetrahedron Lett.* **1994**, *35*, 1965-1968.
5. Eckhardt, M.; Brückner, R. *Angew. Chem.* **1996**, *108*, 1185-1188; *Angew. Chem. Int. Ed. Engl.* **1996**, *35*, 1093-1096; Eckhardt, M.; Brückner, R. *Liebigs Ann. / Recueil* **1997**, 947-959.
6. Ferri, F.; Brückner, R. *Liebigs Ann. / Recueil* **1997**, 961-965.

7. The total synthesis of the aglycon of **1** has now also been achieved: Myers, A. G.; Hammond, M.; Wu, Y.; Xiang, J.–N.; Harrington, P. M.; Kuo, E. Y. *J. Am. Chem. Soc.* **1996**, *118*, 10006-10007.
8. All new compounds gave satisfactory ^{1}H NMR, ^{13}C NMR, and IR spectra. Of compounds **7-8** and **12-14** correct combustion analyses were obtained, of **22** and **23** correct high-resolution mass spectra, and of **17-21** and **24** DCI (NH_4^+) mass spectra which proved the molecular masses.
9. Brickmann, K.; *Dissertation*, Universität Göttingen, **1995**. The methylether analogue of silylether **7** was prepared similarly: Brickmann, K.; Hambloch, F.; Suffert, J.; Brückner, R. *Liebigs Ann.* **1996**, 457-471.
10. Cunico, R. F.; Nair, S. N. *Tetrahedron Lett.* **1997**, *38*, 25-28.
11. Method: Sonogashira, K.; Tohde, Y.; Hagihara, N. *Tetrahedron Lett.* **1975**, 4467-4470.
12. Method: Johnson, C. R.; Adams, J. P.; Braun, M. P.; Senanayake, C. B. W.; Wovkulich, P. M.; Uskokovic, M. R. *Tetrahedron Lett.* **1992**, *33*, 917-918.
13. Audia, J. S.; Boisvert, L.; Patten, A. D.; Villalobos, A.; Danishefsky, S. J. *J. Org. Chem.* **1989**, *54*, 3738-3740.
14. Dess, D. B.; Martin, J. C. *J. Org. Chem.* **1983**, *48*, 4155-4156.
15. Method: McMurry, J. E. *Chem. Rev.* **1989**, *89*, 1513-1524; Robertson G. M. in *Vol. 3* (G. Pattenden, Ed.) of *Comprehensive Organic Synthesis* (Trost, B. M.; Fleming, I. Eds.), Pergamon Press, Oxford, **1991**, 563-611; Lectka, T. in *Active Metals* (Fürstner, A. Ed.), VCH, Weinheim, **1996**, 85-131.
16. *(tert-Butyldimethylsiloxy)-5,6-benzobicyclo[8.4.0]tetradeca-1(14),5,9-triene-2,7-diyne* (**22**): $TiCl_3$ [2.523 g, 16.2 mmol (= 62 mmol per mmol of **20**)] was refluxed in oxygen-free DME (32 ml) for 36 h. After cooling to room temp. blue crystals precipated overnight. Cu/Zn pair (*Tetrahedron Lett.* **1989**, *30*, 1169-) [3.362 g, 47.6 mmol (= 183 mmol per mmol of **20**)] was added to this mixture which was heated to reflux for 6 h under stirring. The temperature was lowered to 30°C. Ketoaldehyde **20** (102 mg, 0.260 mmol) in DME (30 ml) was added via a syringe pump over a period of 4 h. One continued stirring for 45 min, quenched with satd. $NaHCO_3$ solution (50 ml), removed inorganic salts by filtration through Celite, extracted the aqueous layer of the biphasic filtrate with Et_2O (3 x 50 ml), and dried the combined organic phases over Na_2SO_4. Flash chromatography (pentane/Et_2O, 300:1) of the crude product on silica gave the title compound (22 mg, 17%).– ^{1}H NMR (300 MHz, C_6D_6): δ = 0.23 and 0.28 [2 s, $Si(CH_3)_2$], 1.01 [s, $SiC(CH_3)_3$], 1.26 (m_c, presumably interpretable as tt, $J_{12,13} \approx J_{12,11} \approx 6.3$, 12-$H_2$), 1.70 (td, $J_{13,12} \approx J_{13,14} \approx$ 5.5, 13-H_2), 1.95 (m_c, presumably interpretable as td, $J_{11,12} = 6.2$, $J_{11,9} = 1.8$, 11-H_2), 5.45 and 5.87 (m_c and s, 4-H, 9-H), 6.09 (br. t, $J_{14,13} = 4.4$, 14-H), 6.91 and 7.05 (2 td, $^{3}J_o = 7.5$ / $^{4}J_m = 1.1$ and $^{3}J_o = 7.7$ / $^{4}J_m$ = 1.4, respectively, 2'-H, 3'-H), 7.41 and 7.55 (dd and br. d, $^{3}J_o = 7.5$ / $^{4}J_m = 1.1$ and $^{3}J_o = 7.6$, respectively, 1'-H, 4'-H).– ^{13}C NMR (126 MHz, C_6D_6): δ = -4.48 and -3.87 [$Si(CH_3)_2$], 18.53 [$SiC(CH_3)_3$], 22.51, 26.31, and 33.36 (C-11, C-12, C-13), 26.10 [$SiC(CH_3)_3$], 65.70 (C-4), 86.47, 90.00, 96.13, and 96.28 (C-2, C-3, C-7, C-8), 106.37 (C-9), 121.94 and 122.27 (C-1, C-6), 127.61, 128.30 (superimposed by C_6D_5H), 128.67 and 131.73 (C-1', C-2', C-3', C-4'), 140.09 (C-14), 140.38 and 145.18 (C-5, C-10).– IR (C_6D_6): ν = 3230, 2930, 2855, 2360, 2265, 1615, 1450, 1330, 1255, 1160, 1070, 810 cm^{-1} .– $C_{24}H_{28}OSi$ [M^+]: calcd. 360.1909; exact molecular mass (±2 ppm; R = ca. 10000) checked by EI-HRMS (70 eV).
17. *(tert-Butyldimethylsiloxy)-5,6-benzobicyclo[8.4.0]tetradeca-5,10(11)-diene-3,8-diyne-1,2-diol* (**23**; 126 mg, 60%) was prepared at -20°C from keto aldehyde **20** (210 mg, 0.535 mmol) similarly as **22**.– ^{1}H NMR (300 MHz, $CDCl_3$; integrals always referred to *one* diastereomer): δ = 0.20 and 0.22 [2 s, $Si(CH_3)_2$], 0.96 [s, $SiC(CH_3)_3$], [1.53-1.70 and 1.70-1.86 (2 m à 2 H and 1 H), 2.12-2.20 (m, 2 H), 2.35-2.42 (m, 1 H), 12-H_2, 13-H_2, 14-H_2], 2.85 and 3.04 (2 very br. s, 1-OH, 2-OH), 4.56 (s, 2-H), 5.72 (s, 7-H), 6.22 (t, $J_{11,12}$ = 4.0, 11-H), 7.23 and 7.36 (incompletely resolved td and td, $^{3}J_o = 7.5$ / $^{4}J_m = 0.7$ and $^{3}J_o = 7.8$ / $^{4}J_m = 1.5$, respectively, 2'-H, 3'-H), 7.43 and 7.56 (dd and d, $^{3}J_o = 7.7$ / $^{4}J_m = 1.3$ and $^{3}J_o = 8.2$, respectively, 1'-H, 4'-H).– ^{13}C NMR (ATP spectrum at 50 MHz, $CDCl_3$): δ = "+" -4.75 and "+" -4.20 [$Si(CH_3)_2$], "-" 18.32 [$SiC(CH_3)_3$], "-" 18.86, "-" 25.64, and"-" 29.94 (C-12, C-13, C-14), "+" 25.84 [$SiC(CH_3)_3$], "+" 63.69 and "+" 67.28 (C-2, C-7), "-" 72.66 (C-1), "-" 85.04, "-" 87.29, "-" 91.60, and "-" 94.77 (C-3, C-4, C-8, C-9), "-" 119.52 and "-" 123.69 (C-5, C-10), "+" 127.37*, "+" 128.86, "+" 133.30, and "+" 137.69 (4 signals for 5 sp^2-C; C-11, C-1', C-2', C-3', and C-4'), "-" 140.85 (C-6); *relative intensity indicates *two* sp^2-C.– No IR spectrum recorded because of poor solubility.– $C_{24}H_{30}O_3Si$ [M^+]: calcd. 394.1964; exact molecular mass (±2 ppm; R = ca. 10000) checked by EI-HRMS (70 eV).

(*Received in Germany* 21 *July* 1997; *accepted* 29 *August* 1997)