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Synthesis of a New Bicyclic Tetrahydropyridine System Related to Enediyne Antibiotics

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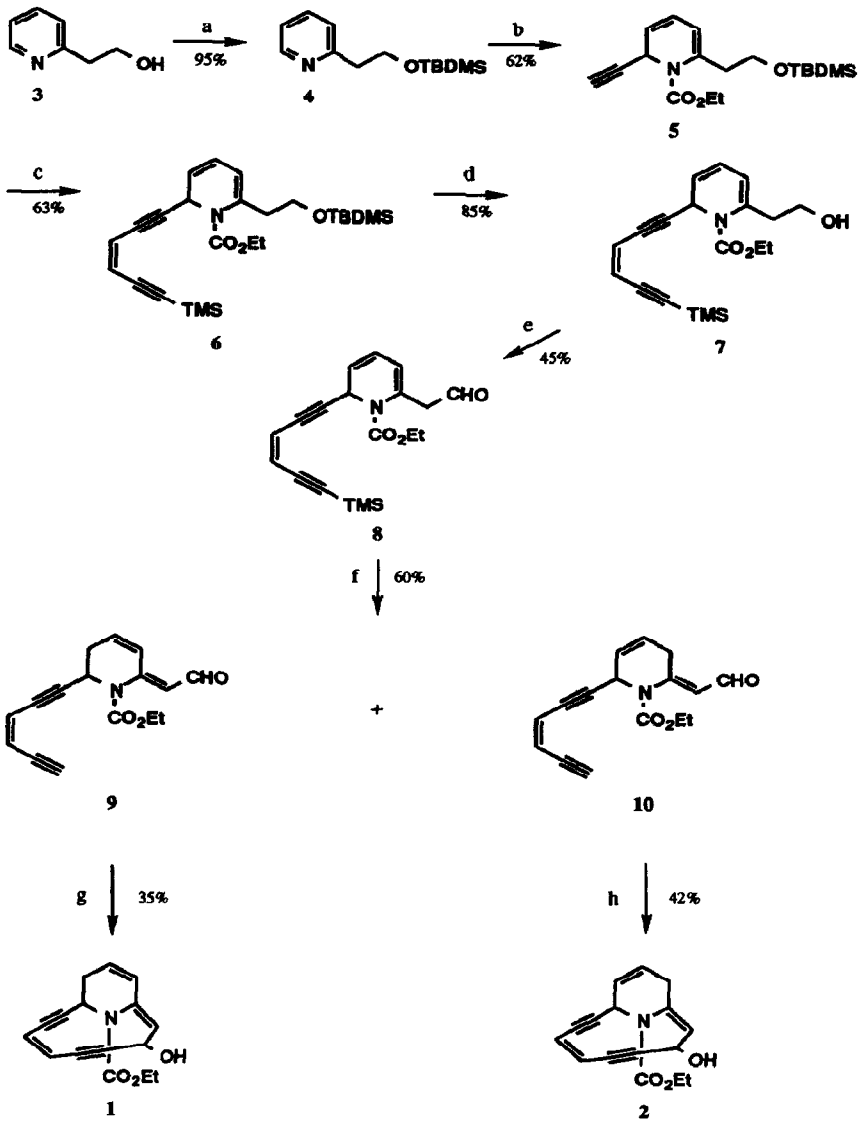
Abstract: The synthesis of model compounds **1** and **2** related to dynemicin A is described.

Enediyne anticancer antibiotics are a rapidly emerging class of compounds derived from natural sources[1]. This family of compounds includes calicheamicin γ_1, esperamicin A_1, neocarzinostatin and dynemicin A as main representatives. Their antitumor activity is due to DNA damage resulting from hydrogen abstraction from the sugar phosphate backbone by a reactive benzenoid diradical[2]. This benzenoid diradical is generated by Bergman type cyclization of the cyclic enediyne system[3].

The high toxicity shown by these compounds prevents their use on clinical treatment[4]. As a consequence, during the last years, a great number of synthetic approaches for the construction of simpler compounds containing this pharmacophore have been published[5]. We contribute to this goal with the synthesis of an enediyne core related to dynemicin A. Most models described, referred to this antibiotic, contain the enediyne system linked to quinoline derivatives, and no model with a pyridine ring as heterocyclic moiety has been reported. We describe herein the synthesis of compounds **1** and **2** , depicted in scheme 1, in which a tetrahydropyridine ring is present.

Silylation of commercially available alcohol **3** gave the t-butyldimethylsilyl ether **4** in 95% yield. Reaction of ethylchloroformate and ethynylmagnesium bromide at 0°C with compound **4** led to the formation of the 1,2-addition product **5** in 62% yield[6]. Castro-Stephans[7] coupling of the acetylene **5** with (Z)-1-chloro-4-trimethylsilyl-1-buten-3-yne[8] was accomplished via Pd(0)-Cu(I) catalysis to provide enediyne **6** in 63% yield. Removal of the silyl group with hydrofluoric acid (85%) followed by oxidation of the alcohol **7** under Swern conditions gave aldehyde **8** in 45% yield. The attempted one pot deprotection-cyclization of **8** with CsF[9] and CsF / 18-crown-6[10] failed to provide the expected cyclized product . During the deprotection of terminal alkyne **8** with potassium fluoride[11], an spontaneous allylic transposition occurred giving rise to the conjugated compounds **9** and **10** in 60% yield as a 2:1 mixture (judged by ^{1}H-NMR). Separation of the isomers by silica gel chromatography and detailed study of their spectral data confirmed their structure[12].

Cyclization of both isomers was first essayed by treatment with LDA/THF at -78°C, but after usual workup only starting material was recovered.

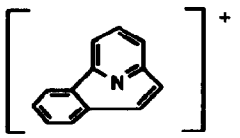


Scheme 1

a) TBDMSCl, Imidazole, DMF, 25°C, 24h. b) $EtCO_2Cl$, HC≡CMgBr, THF, -20°C--0°C, 3h. c) cis- ClCH=CHC≡CTMS (11), CuI, $Pd(PPh_3)_4$, $^nBuNH_2$, Toluene, 25°C, 6h. d) HF, CH_3CN, 25°C, 8h. e) $(COCl)_2$, DMSO, CH_2Cl_2, Et_3N, -60°C, 7h. f) KF, DMF, H_2O, 25°C, 3h. g) $LiN(SiMe_3)_2$, $CeCl_3$, THF, -78°C, 6h. h) $KN(SiMe_3)_2$, THF, -78°C, 1h.

The cyclization was finally achieved by addition of 1.2 eq. of $KN(SiMe3)_2$ to the corresponding aldehyde in THF at -78°C[13]. The resulting compounds **1** and **2** were obtained in 10% and 42% yield respectively, and were spectroscopically fully characterized[14]. Of the two possible racemics that can be formed, only the more stable was isolated (molecular models). Cyclization yield for compound **1** was improved when $LiN(SiMe3)_2$ in the presence of $CeCl_3$ was used[15] (35%).

The presence of a peak (m/z 178) in the mas spectra of compounds **1** and **2** during the electronic impact process, that was assigned to the fragment ion **12** (- H), prompted us to think about the possibility of these compounds to suffer Bergman cycloaromatization.



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In vitro cytotoxicity assays of **1** and **2** have not been performed due to the high instability of both compounds. Polymerization is observed after one day at room temperature. Further studies toward the synthesis of more complex and more stable derivatives linked to a carrier with high affinity to DNA are in progress in our laboratories.

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References and Notes

1. For a review see: (a) Nicolaou, K.C.; Dai, W.-M. *Angew. Chem. Int. Ed. Engl.* **1991**, *30*, 1387. (b) Nicolaou, K.C.; Dai, W.-M.; Tsay, S.-C.; Estevez, V.A.; Wrasidlo, W. *Science* **1992**, *256*, 1172, and references therein.
2. (a) Bergman, R.G. *Acc. Chem. Res.* **1973**, *6*, 25. (b) Jones, R.R.; Bergman, R.G. *J. Am. Chem. Soc.* **1972**, *94*, 660.
3. Lee, M.D.; Dunne, T.S.; Siegel, M.M.; Chang, C.C.; Morton, G.O.; Borders, D.B. *J. Am. Chem. Soc.* **1987**, *109*, 3464.
4. Kadow, J.F.; Cook, D.J.; Doyle, T.W.; Langley, D.R.; Pham, K.M.; Vyas, D.M.; Wittman, M.D. *Tetrahedron* **1994**, *50*, 1519.
5. (a) Nicolaou, K.C.; Smith, A.L.; Wendeborn, S.V.; Hwang, C.-K. *J. Am. Chem. Soc.* **1991**, *113*, 3106. (b) Nishikaw, T.; Ino, A.; Isobe, M. *Tetrahedron*, **1994**, *50*, 1449. (c) Takahashi, T.; Tanaka, H.; Hirai, Y.; Doi, T.; Yamada, H.; Shiraki, T.; Sugiura, Y. *Angew. Chem. Int. Ed. Engl.* **1993**, *32*, 1657.
6. Yamaguchi,R.; Nakazono,Y.; Kawanishi, M. *Tetrahedron Lett.* **1983**, *24*, 1801.

7. (a) Stephans, R.D.; Castro, C.E. *J. Org. Chem.* **1963**, *28*, 3313. (b) Ratovelomanana, V.; Linstrumelle, G. *Tetrahedron Lett.* **1981**, *22*, 315. (c) Guillerm, D.; Linstrumelle, G. *Tetrahedron Lett.* **1985**, *26*, 3811.

8. The cis-chloroenyne **11** was prepared by coupling of TMS-C≡C-H and Z-ClCH=CHCl using $Pd(PPh_3)_4$ / CuI / $^nBuNH_2$ catalysis with 63% yield. (see reference 5c).

9. Wender, P.A.; Zercher, C.K. *J. Am. Chem. Soc.* **1991**, *113*, 2311.

10. Nishikawa, T.; Ino, A.; Isobe, M.; Goto, T. *Chemistry Lett.* **1991**, 1271.

11. Boger, D.L.; Zhou, J. *J. Org. Chem.* **1993**, *58*, 3018.

12. Compound **9**: IR (film) ν: 3280, 2980, 2180, 1700, 1640, 1560, 1420, 1380, 1290, 1260, 1150, 1100, 1060, 760 cm^{-1}. ^{1}H-NMR ($CDCl_3$, 200 MHz) δ: 1.33 (t, 3H, J=7.1 Hz, -CH_2-$\underline{CH_3}$), 2.49-2.87 (m, 2H, -CH_2), 3.25 (d, 1H, J=1.6 Hz, ≡CH), 4.23-4.34 (m, 2H, -$\underline{CH_2}$-CH_3), 5.73-5.87 (m, 3H, H_2,2$H_{olef.}$), 6.22-6.33 (m, 1H, H_4), 6.41 (d, 1H, J=7.5 Hz, =$\underline{CH}$-CHO), 7.14 (dd, 1H, J=10.2, 2.9 Hz, H_5), 10.14 (d, 1H, J=7.5 Hz, -CHO). ^{13}C-NMR ($CDCl_3$, 50 MHz) δ: 14.3, 31.3, 44.7, 63.3, 79.9, 80.3, 85.0, 94.3, 118.6, 119.9, 120.5, 120.7, 131.6, 147.7, 153.1, 189.6. M.S. (EI) m/z (%): 269 (M^+,6), 240 (43), 224 (6), 212 (24), 196 (76), 180 (30), 167 (100), 152 (75), 141 (53), 136 (49), 115 (53), 102 (25), 89 (27), 77 (33), 65 (39), 63 (40).
Compound **10**: IR (film) ν: 3280, 2980, 2090, 1700, 1660, 1630, 1400, 1370, 1300, 1250, 1110, 1070, 1020, 900, 840, 760 cm^{-1}. ^{1}H-NMR ($CDCl_3$, 200 MHz) δ: 1.33 (t, 3H, J=7.1 Hz, -CH_2-$\underline{CH_3}$), 2.41-2.88 (m, 2H, -CH_2), 3.24 (d, 1H, J=1.6 Hz, ≡CH), 4.05-4.35 (m, 2H, -$\underline{CH_2}$-CH_3), 5.74-5.87 (m, 4H, 2$H_{olef.}$, H_4, =CH), 6.12-6.28 (m, 2H, H_2, H_5), 9.69 (d, 1H, J=7.7 Hz, -CHO). ^{13}C-NMR ($CDCl_3$, 50 MHz) δ: 14.1, 38.8, 44.9, 63.4, 80.2, 85.1, 93.9, 119.5, 120.4, 122.6, 128.2, 131.8, 153.5, 190.8. M.S. (EI) m/z (%): 269 (M^+,7), 240 (43), 224 (6), 212 (23), 196 (83), 181 (21), 167 (100), 152 (77), 141 (49), 136 (54), 115 (46), 102 (20), 89 (24), 77 (31), 65 (33), 63 (31).

13. Danishefsky, S.J.; Mantlo, N.B.; Yamashita D.S.; Schulte, G. *J. Am. Chem. Soc.* **1988**, *110*, 6890.

14. Compound **1**: IR (film) ν: 3600-3200 (br), 2920, 1680, 1420, 1370, 1300, 1080, 1020, 740 cm^{-1}. ^{1}H-NMR ($CDCl_3$, 200 MHz) δ: 1.28 (t, 3H, J=7.1 Hz, -CH_2-$\underline{CH_3}$), 2.20-2.89 (m, 2H, -CH_2),4.07-4.28 (m, 2H, -$\underline{CH_2}$-CH_3), 5.46-5.92 (m, 6H, 2$H_{olef.}$, 2H_{ring}, =CH-$\underline{CH}$OH, =$\underline{CH}$-CHOH), 6.39 (dd, 1H, J=10.2, 2.7 Hz, H_5). ^{13}C-NMR ($CDCl_3$, 50 MHz) δ: 14.5, 31.8, 46.7, 60.7, 62.1, 83.6, 86.8, 95.4, 99.6, 120.8, 122.2, 122.8, 125.4, 128.2, 131.6, 153.1. M.S. (EI) m/z (%): 269 (M^+,49), 240 (12), 221 (9), 196 (39), 178 (28), 167 (53), 111 (33), 83 (53), 57 (100).
Compound **2**: IR (film) ν: 3600-3200 (br), 2980, 1680, 1410, 1320, 1260, 1080, 740 cm^{-1}. ^{1}H-NMR ($CDCl_3$, 200 MHz) δ: 1.31 (t, 3H, J=7.1 Hz, -CH_2-$\underline{CH_3}$), 2.17-2.78 (m, 2H, -CH_2), 4.20-4.30 (m, 2H, -$\underline{CH_2}$-CH_3), 5.30-5.85 (m, 6H, 2$H_{olef.}$, 3H_{ring}, =CH-$\underline{CH}$-OH), 6.12 (dd, 1H, J=10.1, 2.6 Hz, =$\underline{CH}$-CH-OH). ^{13}C-NMR ($CDCl_3$, 50 MHz) δ: 14.5, 28.7, 44.9, 60.4, 62.5, 83.0, 84.8, 97.5, 100.6, 121.5, 124.8, 127.0, 128.1, 128.9, 131.4, 153.0. M.S. (EI) m/z (%): 269 (M^+,18), 251 (42), 240 (5), 222 (12), 206 (6), 196 (27), 178 (100), 167 (31), 152 (66).

15. Imamoto, T.; Sugiura, Y.; Takiyama, N. *Tetrahedron Lett.* **1984**, *25*, 4233.

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