Synthesis and Reactivity of Novel Fluorinated Tricyclic Dynemicin A Mimic

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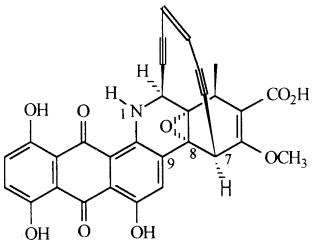
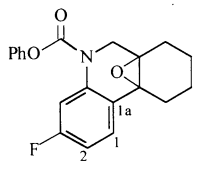
Dynemicin A (**1**) is a potent antitumor antibiotic isolated from fermentation broth *micromonospora chersina*.[1] The pronounced cytotoxic activity of this compound has been attributed to its ability to undergo Bergman cyclization to give a phenylene diradical which initiates DNA cleavage.[2] Cycloaromatization of **1** is triggered by epoxide opening induced by developing electron density at C9.[3] In the previous papers, we reported the substituent effect for epoxide opening with simple model compounds.[4] For instance, compound **2** with fluorine at C3 showed higher electron density at C1a position and faster epoxide opening than unsubstituted one under acidic conditions. This result suggested the possibility that the tricyclic compound with fluorine at C3 could be developed as a new enediyne anticancer drug. In this paper, we describe the synthesis and acid-induced Bergman cyclization of a new enediyne compound with fluorine at C3.



Dynemicin A (**1**)



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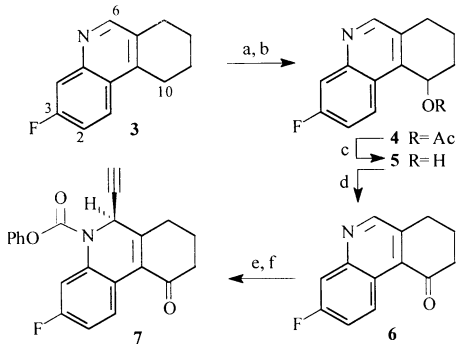
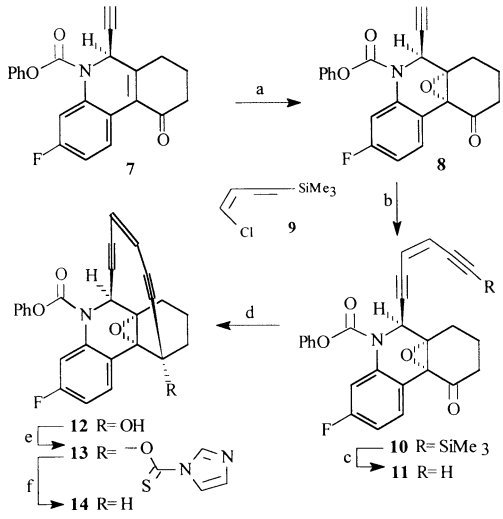
Scheme 1 and 2 summarize the construction of a new enediyne compound **14** related to dynemicin A according to a modified procedure of a typical preparation method.[5] H_2O_2 oxidation and subsequent acetylation with acetic anhydride of 3-fluoro-7,8,9,10-tetrahydrophenanthridine (**3**)[4a] gave acetate **4** (Scheme 1). This acetate was hydrolyzed to alcohol **5** and then, oxidized to ketone **6**. Continuously, introduction of acetylene moiety at the C6 and the N5 protection led to **7** *via* silylation and desilylation. The treatment of the enone **7** with *m*CPBA yielded the epoxy ketone **8** (Scheme 2). Coupling of compound **8** and vinyl chloride **9** using Pd(0)-Cu(I) catalysis afforded an enediyne product **10**.

Desilylation of **10** with $AgNO_3$-KCN produced compound **11**, which was cyclized to give the 10-membered enediyne adduct **12** through treatment with lithium diisopropylamide (LDA). Finally, the desired compound **14**[6] was obtained by the treatment of **12** with thiocarbonyldiimidazole followed by subsequent reduction of the imidazolide **13** with tributyltinhydride ($^nBu_3SnH$) in the presence of a catalytic amount of 2,2'-azobis(isobutyronitrile) (AIBN).

Acid-induced epoxide opening and Bergman cyclization

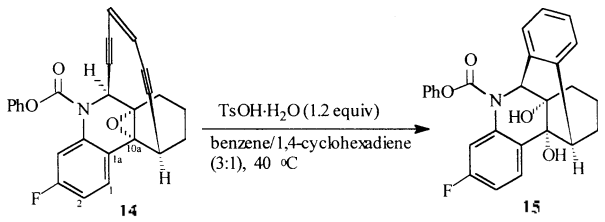


Scheme 1. C6 and C10 functionalization of tricyclic compound. Reagents and conditions: (a) 2.0 equiv of H_2O_2, AcOH, 70 °C, 8h, 78%; (b) Ac_2O, 25 °C, 2 h, 90%; (c) K_2CO_3 (cat.), MeOH, 25 °C, 5 h, 78%; (d) 1.5 equiv of PCC, CH_2Cl_2, 0 °C, 3h, 87%; (e) 1.2 equiv of $^tBuMe_2SiOSO_2CF_3$, 1.5 equiv of Et_3N, CH_2Cl_2, 25 °C, 3h, 94%; (f) 1.2 equiv of ethynylmagnesium bromide, 1.1 equiv of PhOCOCl, THF, -78 °C to 25 °C, 40 min and then, 10% HCl, 25 °C, 12h, 100%.



Scheme 2. Synthesis of a new dynemicin A model **14**. Reagents and conditions: (a) 1.2 equiv of *m*CPBA, aq. $NaHCO_3$/CH_2Cl_2, 25 °C, 30 min, 64%; (b) 1.6 equiv of **9**, 0.06 equiv of $Pd(PPh_3)_4$, 0.24 equiv of CuI, 2.0 equiv of $nBuNH_2$, benzene, 25 °C, 1 h, 80%; (c) 4.0 equiv of $AgNO_3$, 7.0 equiv of KCN, THF/EtOH/H_2O, 25 °C, 25 min, 86%; (d) 1.0 equiv of LDA, toluene, -78 °C, 10 min, 75%; (e) 3.0 equiv of thiocarbonyldiimidazole, 0.6 equiv of DMAP, CH_2Cl_2, 25 °C, 24 h, 56%; (f) 2.0 equiv of $^nBu_3SnH$, AIBN (cat.), toluene, 80 °C, 1h, 83%.

for new model compound **14** was performed to probe the possibility as a new enediyne anticancer drug. (Scheme 3). Treatment of **14** with p-toluenesulfonic acid monohydrate ($TsOH \cdot H_2O$) at 40 °C gave the aromatized product **15**[7] *via*



Scheme 3. Acid-induced Bergman cyclization of new compound.

epoxide opening in a quantitative yield. Expectedly, the reaction time was 25 min which was much faster than that of unsubstituted compound under the same reaction conditions.[8] This result suggests that the stimulated Bergman cyclization through fluorine substitution at C3 could lead to potential activation as a drug.

Our experimental result spurred for us to proceed further synthesis which would be applied on biological test. Presently, the transformation of N5 protection in **14** which is easily removed under basic conditions is undergoing .

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References

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6. Spectroscopic data for compound **14**. IR ($CHCl_3$): ν_{max}= 3070, 2970, 2880, 2200, 1720, 1465, 1380, 1200; ^1H NMR (300 MHz, DMSO-d_6): δ= 7.49 (dd, J = 8.9, 6.2 Hz, 1H, aromatic), 7.47-7.39 (m, 3H, aromatic), 7.31-7.19 (m, 3H, aromatic), 7.14 (td, J = 8.6, 3.9 Hz, 1H, aromatic), 6.05 (dd, J = 9.9, 1.4 Hz, 1H, olefinic), 5.93 (dd, J = 9.9, 1.6 Hz, 1H, olefinic), 5.57 (br s, 1H, *CH*N), 4.07 (br s, 1H, CH_2CH), 2.35 (dd, J = 15.5, 7.4 Hz, 1H, CH_2), 2.21-2.10 (m, 1H, CH_2), 1.89-1.72 (m, 3H, CH_2CH_2), 1.61-1.53 (m, 1H, CH_2); ^{13}C NMR (75 MHz, DMSO-d_6): δ= 161.2 ($^1J_{C-F}$ = 242 Hz), 152.2, 150.5, 136.5, 129.4, 129.3, 125.9, 125.8, 124.9, 122.2, 121.6, 113.1, 112.3, 102.3, 93.4, 91.0, 89.0, 69.5, 60.2, 49.2, 28.6, 22.7, 22.1, 15.2.
7. Spectroscopic data for compound **15**. IR ($CHCl_3$): ν_{max}= 3460, 3080, 2940, 1710, 1500, 1380, 1200; ^1H NMR (500 MHz, DMSO-d_6): δ= 7.81 (d, J = 8.4 Hz, 1H, aromatic), 7.64 (d, J = 6.8 Hz, 1H, aromatic), 7.62 (d, J = 6.8 Hz, 1H, aromatic), 7.48-7.45 (m, 3H, aromatic), 7.31-7.27 (m, 2H, aromatic), 7.22 (t, J = 6.8 Hz, 1H, aromatic), 7.15 (t, J = 6.8 Hz, 1H, aromatic), 6.94 (d, J = 7.4 Hz, 1H, aromatic), 6.89 (td, J = 8.4, 2.6 Hz, 1H, aromatic), 5.65 (br s, 1H, *CH*N), 5.22 (br s, 1H, *OH*), 5.10 (br s, 1H, *OH*), 3.18 (br s, 1H, CH_2CH), 2.28-2.21 (m, 1H, CH_2CH_2), 2.12-2.06 (m, 1H, CH_2CH_2), 1.74-1.71 (m, 1H, CH_2CH_2), 1.36-1.31 (m, 1H, CH_2CH_2), 1.25-1.22 (m, 2H, CH_2CH_2); ^{13}C NMR (125.8 MHz, DMSO-d_6): δ= 160.3 ($^1J_{C-F}$ = 240 Hz), 151.0, 144.5, 139.2, 135.7, 133.7, 133.0, 129.9, 129.3, 128.3, 128.0, 127.5, 127.2, 126.7, 125.5, 124.5, 121.8, 80.7, 64.8, 64.4, 51.7, 39.0, 26.5, 18.2.
8. The reacion time for unsubstituted model compound was 80 minutes. See 5c for details.