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# A Facile Synthesis of Spin Labeled *4′-Epi-N*-Trifuoroactyldaunomycin Derivatives

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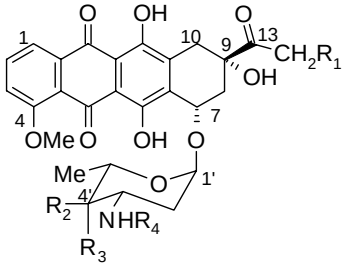
**Abstract:** The spin labeled *4′-Epi-N*-trifuoroacetyldaunomycin derivatives **6-7** were conveniently synthesized from daunomycin in middle yield. The key steps were the protection of compd. **5** at 9-position and nucleophilic displacement of **5** with R·COOH and DBU at room temperature.

**Keywords:** Spin labeled, daunomycin, antitumor, synthesis.

The anthracycline antibiotics, such as daunomycin **1** and doxorubicin **2**, have attracted considerable interest because of their great therapeutic value in treating a number of human cancers. However, their use has been limited by a number of toxic and undesirable side effects and this stimulated the search for new anthracyclines with improved pharmacological profiles[1,2,3]. In our group, nitroxy radicals were first introduced to the sugar moieties of **1** and **2**, and some exhibited significant antitumor activity with a significant decrease in the toxicity[4,5]. As a part of ongoing medicinal chemistry program in the anthracycline antibiotics area, here we reported a new practice and facile synthesis of the spin labeled *4′-epi-N*-trifuoroacetyldaunomycin derivatives **6-7** directly from **4** as shown in **Scheme 1**.

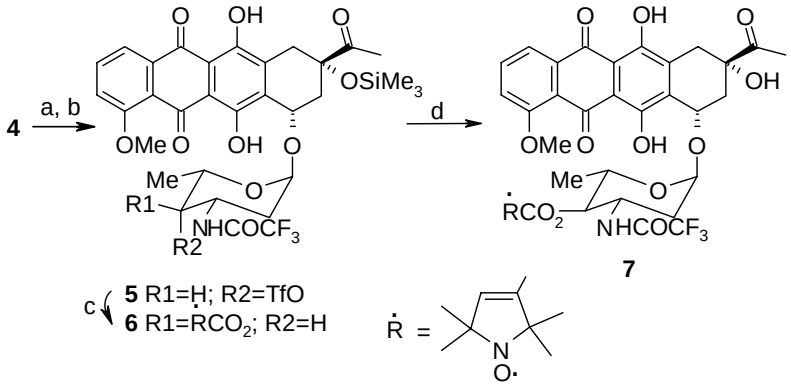
*N*-trifuoroacetyldaunomycin **4** was obtained from daunomycin **1** upon treatment with trifluoroacetic anhydride according to our previous process[6]. Esterification of **4** with trifluoromethanesulfonic anhydride and pyridine, followed protection of hydroxy group at 9-position with *N*, *O*-bis (trimethyl)acetamide to give **5** in quantitative yield[7]; without isolation, compound **6** was synthesized by nucleophilic displacement[8] of **5** with RCOOH and DBU in 75% yield. Deportection of **6** with KF-AcOH-$Et_3N$ under mild condition, affording compound **7** in 95% yield. The structures of **6** and **7** were




**1** $R_1$=$R_2$=$R_4$=H, $R_3$=OH
**2** $R_1$=$R_3$=OH, $R_2$=$R_4$=H
**3** $R_1$=$R_3$=H, $R_2$=OH, $R_4$=$COCF_3$
**4** $R_1$=$R_2$=H, $R_3$=OH, $R_4$=$COCF_3$

confirmed by IR, elemental analysis, ESR and MS[9].

**Scheme 1**




Reagent and conditions: a. $(CF_3SO_2)O$, Py, $CH_2Cl_2$, -5~0°C; b. *N*, *O*-bis(trimethyl) acetamide, r.t.; c. R·COOH, DBU, benzene, r.t., 10 h; d. KF-AcOH-$Et_3N$, r.t.

## References and notes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7. Compound **5** was unstable, it was directly used in next steps. Compd. **5** $^1$H-NMR (500MHz, $CDCl_3$, δ ppm, TMS) 13.98 (s, 1H, 11-OH), 13.40 (s, 1H, 6-OH), 8.03 (d, 1H, J=7.65Hz, H-1), 7.76 (t, 1H, J=8.25Hz, H-2), 7.38 (d, 1H, J=8.10Hz, H-3), 6.17 (d, 1H, J=8.25Hz, $NHCOCF_3$), 5.60 (d, 1H, J=2.62Hz, H-1′), 5.25 (dd, 1H, J=5.30, 6.58Hz, H-7), 4.69 (d, 1H, J=6.42Hz, H-5′), 4.60 (s, 1H, 3'-H), 4.08 (s, 3H, $CH_3O$), 3.76 (m, 1H, H-4′), 3.40 (d, 1H, J=17.83Hz, H-10a), 3.01 (d, 1H, J=17.88Hz, H-10b), 2.41 (m, 1H, H-8a), 2.26 (s, 3H, $CH_3$), 2.21-2.17 (m, 2H, H-8b, H-2a), 1.88 (d, 3H, J=6.60Hz, 5′-$CH_3$), 1.73 (m, 1H, H-2b), 0.12 (s, 9H, $Si(CH_3)_3$).
8. If the hydroxy group at 9-position of compd. **5** was unprotected, unusual rearrangement occurred at the same conditions as shown previously in ref. 10.
9. The spectra data of compd.**7** are the same as reported in ref. 4.
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