SHORT PAPER

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A facial synthesis of 7-selenodaunomycinone derivatives

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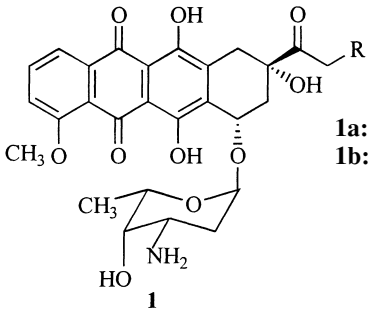
7-selenodaunomycinone derivatives **3a–e** were synthesised by condensation of daunomycinone **2** with aryl selenols catalysed by trifluoroacetic acid in dichloromethane at room temperature. When the concentration of aryl selenol exceeds **2** to 2–3 times, 7-deoxydaunomycinone **4** can be obtained. Also 7*S*-configuration of **3a** can turn into 7*R*-isomer catalysed by boron trifluoride-etherate.

Keywords: 7-selenodaunomycinone derivatives, configuration

Daunorubicin (**1**, R=H, DAU) and doxorubicine (**1**, R=OH, DOX) are clinically useful anthracyclin antitumor agents currently. However, their clinic uses are hampered by a number of undesirable side effects, especially serious cardiotoxicity.[1] The mechanism of antibiotic action of DOX lies its ability intercalate between adjacent DNA base pairs causing topoisomerase II inhibition.[3] DNA binding data and the results of biological testing point out that the groups linked at C-7 and C-9 play an important role in the stabilisation of the cleavable ternary complex drug-DNA-topoisomerase II via specific contacts.[2–4] Therefor, DNA intercalation and inhibition of topoisomerases are regarded as the important ways for anthracyclines acting as antitumor agents[2,4] and structure-modifications of anthracyclines are the best way to win these attempts. Many DAU and DOX derivatives have been synthesised,[5] but most of them maintain the sugar moiety.[6] Few studies have been addressed the attempt of replacing the sugar moiety by other substructures, which might produce new molecules to be more accommodated in the minor groove of DNA,[6] and displacement of 7-OH of daunomycinone by selenium group has not been reported so far. Selenium now was recognised as an essential nutrient and its deficiency can result many diseases in human body, such as cancer,[7,8] cardiovascular disease,[9] loss of immunocompetence,[9] viral infections[9] and so on. So we now reported a facile synthesis of 7-selenodaunomycinone derivatives from displacement of daunomycinone **2** with aryl selenols.



1a: R=H daunorubicin
1b: R=OH doxorubicin

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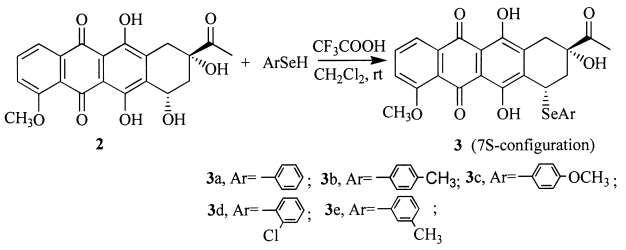
The reaction usually takes place under mild conditions. The following catalysts were carried out: trifluoroacetic acid, boron trifluoride-etherate, *p*-toluenesulfonic acid, zinc chloride, Acetic acid and hydrochloric acid. Trifluoroacetic acid was found to be the most convenient to synthesised 7-selenodaunomycinone derivatives **3a–e** (Scheme 1). In contrast, the reactions catalysed by acetic acid and hydrochloric acid remained unreacted. The experimental results are listed in Table 1.

Table 1 Elemental results of **3**

Compd.	m.p.(oC)	Yield %	Elemental analysis %	
			C	H
3a	187-188.5	64.1	60.37(60.34)	4.11(4.13)
3b	173-175	70.2	61.02(60.98)	4.36(4.39)
3c	167-170	71.7	59.23(59.27)	4.23(4.26)
3d	177.5-181	58.2	56.73(56.71)	3.66(3.70)
3e	168.5-169.5	78.3	60.95(60.98)	4.39(4.39)



2 **3** (7S-configuration)

3a, Ar= ; **3b**, Ar= CH3; **3c**, Ar= OCH3 ;
3d, Ar= Cl; **3e**, Ar= CH3 ;

Scheme 1

In our experiments, only one isomer was obtained. The NMR spectra of compounds **3** show: H-7 as doublet at δ4.87–4.95 having a coupling constant of 2.4-3.6Hz (see spectra data below). According to literature reports[10,11] and comparing with the *J* of daunomycinone **2** (H-7, *J*=3.75Hz), the configuration of **3** was determined as 7*S*-configration.

Interestingly, when the molar ratio of **2** and aryl selenol is 1:1 catalysed by BF_3Et_2O and $ZnCl_2$, aim products **3** can be obtained mainly. When the concentration of aryl selenol exceeds **2** to 2–3 times, however, 7-deoxydaunomycinone **4** was mainly product (Scheme 2). On the other hand, pure **3a** (7*S*-configuration) was tested in the presence of BF_3Et_2O in CH_2Cl_2, **4** was not found but **5** (7*R*-isomer, δ_{ppm} 4.98, dd, H-7, *J*=8.5Hz, *J*=6.05Hz; spectra data are listed below) was obtained mainly (Scheme 2). At same time, benzyl alcohol was reacted with selenophenol catalysed by BF_3Et_2O in CH_2Cl_2, benzyl phenyl selenide was gained (identified by GC–MS). These experiments remind that the formation of **4** is related to aryl selenol, probably as reducer, and anthraquinone, a familiar oxidiser and redox reaction might occur between them. The mechanism studies of this reaction are in the progress.

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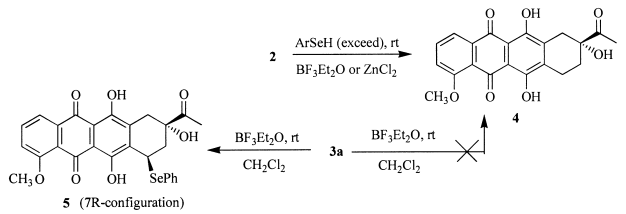
† This is a Short Paper, there is therefore no corresponding material in *J Chem. Research (M).*

Experiment

Melting point was determined on a YANACO melting point apparatus and uncorrected. IR spectra were taken on a Nicolet 230 FT-IR spectrophotometer, elemental analyses on Carlo Elba 1106 instrument, MS spectra on Esquire LC-00075 and NMR spectra on AVANCE DMX500.



Scheme 2

Preparation of **3:** *General procedure:* (with **3a** as an example). To a solution of **2** (41mg, 0.103mmol) in CH_2Cl_2 (10ml) was added selenophenol (19mg, 0.12mmol) and CF_3COOH 0.5ml, stirred at room temperature for 3h, monitored by TLC. The reaction mixture quenched into water, washed with saturated $NaHCO_3$, water, extracted with CH_2Cl_2 (3×25ml). The organic phase was dried with anhydrous Na_2SO_4 and then evaporated in vacuum. The residue was isolated by silica gel column chromatography eluting with hexane/dichloromethane/acetate ether (4:4:1) and **3a** was obtained in the yields of 64.1% (Table 1).

The spectra data of new compounds are listed below

3a: IR (cm^{-1}): 3444, 1695, 1617, 1583; ^{1}H-NMR (δppm): 14.02 (1H, s, OH), 13.40 (1H, s, OH), 8.03 (1H, d, *J* = 7.7Hz, ArH), 7.77 (3H, m, ArH+Ar'H), 7.39 (1H, d, *J* = 8.4Hz, ArH), 7.34 (3H, m, Ar'H), 4.95 (1H, d, *J* = 3.65Hz, H-7), 4.43 (1H, s, OH-9), 4.09 (3H, s, OCH_3), 3.19 (1H, d, *J* = 18.7Hz, H-10e), 3.01 (1H, d, *J* = 18.7Hz, H-10a), 2.55 (1H, dd, *J* = 14.7, 5.15Hz, H-8e), 2.49 (1H, d, *J* = 14.7Hz, H-8a), 2.39 (3H, s, CH_3). ^{13}C-NMR (δppm): 211.69 (C = O), 187.21 (C = O), 186.70 (C = O), 16128 (C-4), 155.98 (C-6), 155.93 (C-11), 137.49 (C-2a), 135.93 (C-6a), 135.80 (C), 135.42 (2×CH), 133.42 (C-12a), 131.47 (C-10a), 129.38 (2×CH), 128.59 (C), 121.22 (C-4a), 119.94 (C-3), 118.53 (C-1), 111.32 (C-5a), 110.70 (C-11a), 77.01 (C-9), 56.95 (OCH_3), 36.69 (C-7), 35.30 (C-8), 33.14 (C-10), 24.72 (CH_3).

3b: IR (cm^{-1}): 3441, 1695, 1618, 1538; ^{1}H-NMR (δppm): 14.04 (1H, s, OH), 13.40 (1H, s, OH), 8.07 (1H, d, *J* = 7.6Hz, ArH), 7.77 (1H, t, *J* = 7.8Hz, ArH), 7.65 (2H, d, *J* = 7.8Hz, Ar'H), 7.38 (1H, d, *J* = 8.20Hz, ArH), 7.14 (2H, d, *J* = 7.8Hz, Ar'H), 4.91 (1H, d, *J* = 2.65Hz, H-7), 4.09 (3H, s, OCH_3), 3.20 (1H, dd, *J* = 18.7, 1.3Hz, H-10e), 3.01 (1H, d, *J* = 18.7Hz, H-10a), 2.48 (1H, dd, *J* = 14.8, 5.0Hz, H-8e), 2.45 (1H, d, *J* = 14.8Hz, H-8a), 2.40 (3H, s, CH_3), 2.36 (3H, s, CH_3). ^{13}C-NMR (δppm): 211.79 (C = O), 187.17 (C = O), 186.64 (C = O), 161.26 (C-4), 155.91 (C-6), 155.84 (C-11), 139.20 (C-2a), 137.27 (C-6a), 135.89 (C), 135.48 (2×CH), 133.51 (C-12a), 130.99 (C-10a), 129.48 (2×CH), 128.48 (C), 121.31 (C-4a), 119.91 (C-3), 118.59 (C-1), 111.30 (C-5a), 110.78 (C-11a), 77.02 (C-9), 56.91 (OCH_3), 35.59 (C-7), 35.02 (C-8), 33.18 (C-10), 24.76 (CH_3), 21.56 (CH_3).

3c: IR (cm^{-1}): 3433, 1695, 1617, 1583; ^{1}H-NMR (δppm): 14.07 (1H, s, OH), 13.40 (1H, s, OH), 8.03 (1H, d, *J* = 7.7Hz, ArH), 7.78 (1H, t, *J* = 8.2Hz, ArH), 7.68 (1H, d, *J* = 8.7Hz, Ar'H), 7.39 (1H, d, *J* = 8.3Hz, ArH), 6.85 (1H, d, *J* = 8.7Hz, Ar'H), 4.87 (1H, d, *J* = 2.4Hz, H-7), 4.60 (1H, s, OH-9), 4.10 (3H, s, OCH_3), 3.81 (3H, s, OCH_3), 3.18 (1H, d, *J* = 18.7Hz, H-10e), 3.01 (1H, d, *J* = 18.7Hz, H-10a), 2.46 (2H, m, H-8), 2.40 (3H, s, CH_3). ^{13}C-NMR (δppm): 211.89 (C = O), 187.18 (C = O), 186.65 (C = O), 161.26 (C-4), 160.46 (C), 156.02 (C-6), 155.86 (C-11), 137.87 (2°¡CH), 137.41 (C-2a), 135.93 (C), 135.74 (C), 135.70 (C-12a), 135.58 (C-10a), 121.28 (C-4a), 119.92 (C-3), 118.50 (C-1), 115.02 (2°¡CH), 111.31 (C-5a), 110.67 (C11a), 77.02 (C-9), 56.95 (OCH_3), 56.54 (OCH_3), 36.08 (C-7), 34.65 (C-8), 33.20 (C-10), 24.80 (CH_3).

3d: IR (cm^{-1}): 3433, 1708, 1617, 1538; ^{1}H-NMR (δppm): 13.77 (1H, s, OH), 13.36 (1H, s, OH), 7.98 (1H, d, *J* = 7.65Hz, ArH), 7.79 (1H, d, *J* = 7.4Hz, Ar'H), 7.74 (1H, t, *J* = 8.0Hz, ArH), 7.45 (1H, d, *J* = 7.8Hz, Ar'H), 7.34 (1H, d, *J* = 8.2Hz, ArH), 7.26 (1H, m, Ar'H), 7.19 (1H, m, Ar'H), 4.94 (1H, d, *J* = 2.4Hz, H-7), 4.10 (1H, s, OH-9), 4.05 (3H, s, OCH3), 3.15 (1H, d, *J* = 18.6Hz, H-10e), 3.01 (1H, d, *J* = 18.6Hz, H-10a), 2.67 (2H, m, H-8), 2.40 (3H, s, CH_3). ^{13}C-NMR (δppm): 211.05 (C = O), 187.10 (C = O), 186.56 (C = O), 161.24 (C-4), 156.27 (C-6), 156.02 (C-11), 138.49 (C-2a), 138.31 (C-6a), 136.73 (CH), 135.90 (C), 135.77 (CH), 133.35 (C-12a), 132.71 (C-10a), 129.73 (CH), 129.45 (CH), 127.33 (C), 121.27 (4a), 119.90 (C-3), 118.47 (C-1), 111.22 (C-5a), 110.50 (C-11a), 76.76 (C-9), 56.93 (OCH_3), 36.39 (C-7), 34.75 (C-8), 32.97 (C-10), 24.47 (CH_3).

3e: IR (cm^{-1}): 3447, 1695, 1617, 1582; ^{1}H-NMR (δppm): 14.00 (1H, s, OH), 13.33 (1H, s, OH), 7.96 (1H, d, *J* = 7.6Hz, ArH), 7.23 (1H, t, *J* = 8.0Hz, ArH), 7.57 (1H, s, Ar'H), 7.53 (1H, d, *J* = 7.6Hz, Ar'H), 7.34 (1H, d, *J* = 8.3Hz, ArH), 7.21 (1H, q, *J* = 7.6Hz, Ar'H), 7.14 (1H, d, *J* = 7.5Hz, Ar'H), 4.91 (1H, d, *J* = 3.6Hz, H-7), 4.06 (3H, s, OCH_3), 3.18 (1H, dd, *J* = 18.6, 1.0Hz, H-10e), 2.95 (1H, d, J = 18.6Hz, H-10a), 2.52 (1H, dd, *J* = 14.8, 5.1Hz, H-8e), 2.46 (1H, d, *J* = 14.8Hz, H-8a), 2.40 (3H, s, CH_3), 2.38 (1H, s, CH_3). ^{13}C-NMR (δppm): 211.89 (C = O), 187.10 (C = O), 186.62 (C = O), 161.26 (C-4), 155.95 (C-6), 155.86 (C-11), 139.22 (C-2a), 137.30 (C-6a), 135.89 (C), 135.73 (C), 133.59 (C-12), 132.36 (CH), 130.99 (C-10a), 129.44 (CH), 129.18 (CH), 128.85 (C), 121.31 (C-4a), 119.89 (C-3), 118.54 (C-1), 111.29 (C-5a), 110.69 (C-11a), 77.10 (C-9), 56.93 (OCH_3), 35.51 (C-7), 34.98 (C-8), 33.15 (C-10), 24.79 (CH_3), 21.55 (CH_3).

5: m.p. 73–75°C; Elemental analysis (%): Found, C: 60.38, H: 4.09; Calcul., C: 60.34, H: 4.13; IR (cm^{-1}): 3443, 1696, 1617, 1583; ^{1}H-NMR (δppm): 14.05 (1H, s, OH), 13.36 (1H, s, OH), 8.00 (1H, d, *J* = 7.54Hz, ArH), 7.75 (1H, t, *J* = 8.0Hz, ArH), 7.42 (2H, d, *J* = 7Hz, Ar'H), 7.36 (2H, m, ArH+Ar'H), 7.25 (2H, m, Ar'H), 4.98 (1H, dd, *J* = 8.5, 6.05Hz, H-7), 4.08 (3H, s, OCH3), 3.68 (1H, s, OH-9), 2.93 (1H, dd, *J* = 16.2, 2.68Hz, H-10e), 2.50 (1H, dd, *J* = 15.4Hz, 5.9Hz, H-8e), 2.32 (2H, m, *J* = 16.2, 2.6, 5.9Hz, H-10a+H-8a), 2.20 (3H, OCH_3). ^{13}C-NMR (δppm): 210.39 (C = O), 187.28 (C = O), 186.73 (C = O), 161.31 (C-4), 155.75 (C-6), 155.61 (C-11), 139.43 (C-2a), 137.28 (2×CH), 136.00 (C-6a), 135.74 (C), 134.08 (C-12a), 131.84 (C-10a), 129.43 (C), 129.26 (2×CH), 123.51 (C-4a), 119.89 (C-3), 118.56 (C-1), 111.72 (C-5a), 110.89 (C-11a), 78.13 (C-9), 56.96 (OCH_3), 38.87 (C-7), 32.39 (C-8), 31.07 (C-10), 24.15 (CH_3).

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