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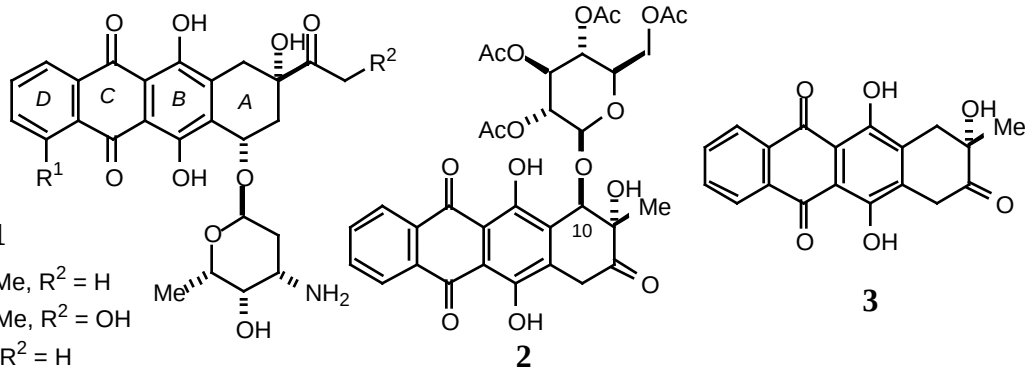
MAINSTREAM OR MEDICINAL CHEMISTRY

Synthesis of *A*-Ring Modified Anthracyclines as Potential Anticancer Agents

Anthracyclines of type **1** are endowed with significant anticancer activity and several representatives, *e.g.* daunomycin **1a**, adriamycin **1b** and idarubicin **1c**, are used clinically.[1,2] One mechanism by which anthracyclines are considered to exert their anticancer action is by binding non-covalently to DNA, preventing the unwinding and thence the replication process. In the binding, the planar *B, C* and *D* rings insert between the base pairs and are held by π-stacking interactions; the *A* ring and the sugar are involved in polar and H-bonding interactions. As part of a programme aimed at determining the effect of *A*-ring modification on anticancer activity, we have recently discovered that certain derivatives of compound **2** are endowed with notable cytotoxic properties. The aim of the project is to prepare related derivatives of compound **3** and thence to define the importance of the 10-substituent.



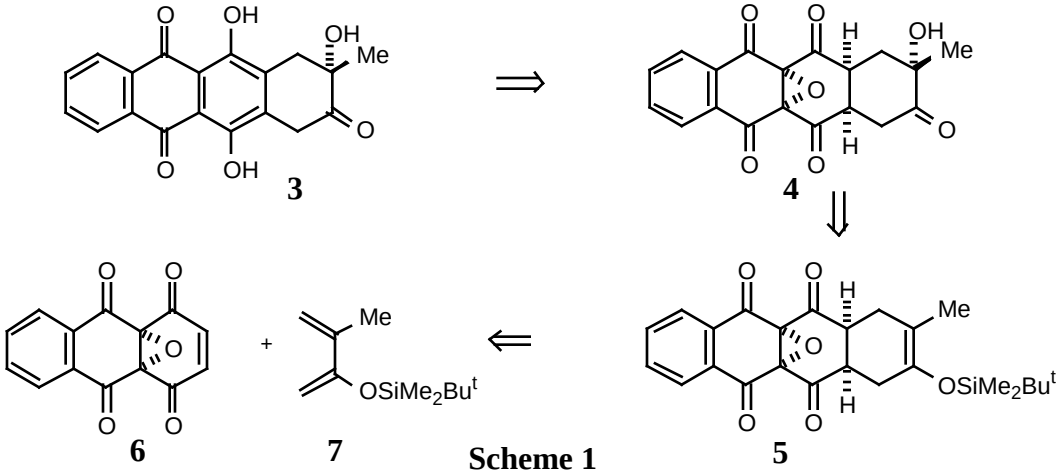
1

a R^1 = OMe, R^2 = H
b R^1 = OMe, R^2 = OH
c R^1 = H, R^2 = H

2

3

In the retrosynthesis, outlined in Scheme 1, it is envisaged that the pre-target **3** (as a racemate) will be accessible from **4** by a reductive aromatisation. In turn, an epoxidation–desilylation sequence should deliver **4** from **5**, the product of an *endo*-selective Diels–Alder reaction of the dienophile **6**[3] and the diene **7**.



3 ⟹ **4** ⇓ **5** ⟸ **6** + **7**

Scheme 1

References

1 *Anthracycline Antibiotics*, ed W Priebe, ACS Symposium Series, **574**, 1995.
2 F Arcamone, *Doxorubicin Anticancer Antibiotics*, Academic Press, 1981.
3 R C Gupta, P A Harland and R J Stoodley, *Tetrahedron*, 1984, **40**, 4657.