COMMUNICATION

A construction of the angularly hydroxylated *cis* 1,8-naphthalenedione system typical of the tetracyclines

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This article is dedicated to Professor Peter Yates on the occasion of his 60th birthday

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This paper demonstrates the feasibility of constructing the angularly hydroxylated 1,8-decalindione system typical of the tetracycline group of antibiotics. The α-hydroxy-β-diketone structure is constructed by the action of fluoride ion on an enediol disilyl ether. The siloxyketone enolate thus generated is then intramolecularly trapped by an appositely placed ester.

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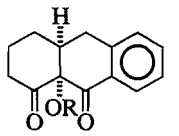
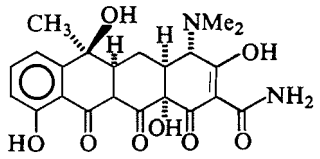
Cet article montre qu'il est possible de construire le système d'une 1,8-décalinedione portant un hydroxyle dans l'angle qui est typique du groupe d'antibiotiques apparentés à la tétracycline. La fonctionalité α-hydroxy β-dicétone est formée par l'action de l'anion fluorure sur le bis-silyl ether d'un ènediol. L'énolate de siloxy cétone ainsi formé est alors piégé intramoléculairement par un ester approprié.

This communication reports the construction of a molecule **1** (as its trimethylsilyl ether **1***a*) embodying the α-hydroxy-β-diketone array which is a common feature of the a/b ring system of antibiotics such as tetracycline, **2** (1). Our goal was to develop a process which would specifically produce the *cis*-fused 8a-hydroxy-1, 8-napthalenedione arrangement rather than the mixture of *cis* and *trans* isomers which results when the hydroxydiketone construction depends, as it classically has (2), on the hydroxylation of a precursor enolic β-diketone system.



1 R = H

1*a* R = Si



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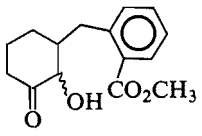

3

We envisaged that a cyclization formally represented by **3** → **1** would, if feasible, lead to the required structure and stereochemistry, as a result of well-understood geometric constraints on the transition state for the cyclization process.

Our initial attempts were centered on the possibility of achieving base-catalyzed cyclization of some enolate species derivable from ketols like **3**. The ketol **3** was simply constructed by alkylation of the isobutyl enol ether of cyclohexane-1,2-dione with methyl 2-bromomethylbenzoate (LDA–THF; HMPA, 1 h, −20°C) to **4** (61% yield), which was then transformed to the desired **3** by reduction with sodium borohydride followed by hydrolysis of the enol ether with 50% acetic acid.

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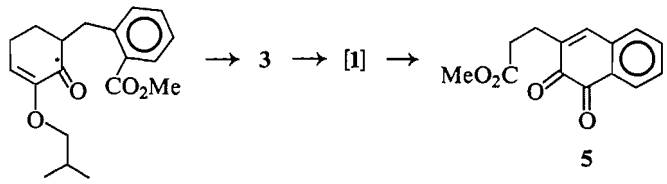
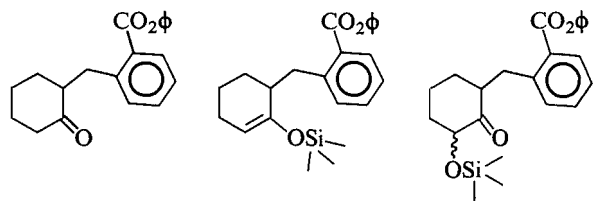


4 → **3** → [1] → **5**

Treatment of the ketol **3** with 1 equiv. of sodium hydride in THF for 2 h at room temperature resulted in the isolation, after flash chromatography, of the α-naphthoquinone **5** as orange crystals, mp 89.5–91.5°C; ir ($CHCl_3$): 1735 (s), 1695 (w), 1662 (s), 1627 (w) cm^{-1}; nmr (δ): 1.67–2.02 (m, 2H), 2.10–2.55 (m, 4H), 3.60 (s, 3H), 6.85–7.65 (m, 4H), 7.87–8.06 (m, 1H); ms (EI): 258. This result strongly suggests that the desired cyclization (**3** → **1**) had taken place but had been followed by cleavage of the β-diketone system and air oxidation (the latter, presumably, during chromatography).

The desired cyclization was finally achieved by a modification of the general scheme above.

Alkylation of cyclohexanone (LDA/THF/−78°C) with phenyl-2-bromomethylbenzoate (HMPA, −10°C) gave **6**, mp 70–71.5°C in 76% yield. The silyl enol ether **7** (75%) obtained via kinetic deprotonation with LDA[2] was converted to the ketol TMS ether **8** (*m*-CPBA; TMSCl, NEt_3; ~2:1 mixture of stereoisomers, 82% yield) (3).



6 **7** **8**

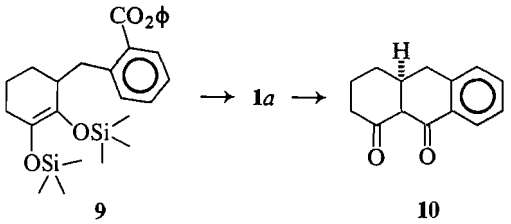
After various attempts at cyclization of the kinetic lithium enolate of **8** had met with failure, success was finally achieved

[2] About 20% of the tricyclic enol lactone, mp 104.5°C, derived from the enolate precursor of **7** was also obtained.

by the use of the crucial silylated enediol **9**[3] obtained from the kinetic enolate of **8**: Treatment of **9** with a dry (molecular sieves) THF solution of tetrabutylammonium fluoride at −78 to −20°C, followed by quenching with *N*-trimethylsilylimidazole, gave **1***a* in 74% yield (mp 69.5–70°C from hexane; ir (neat): 1735 (s), 1725 (s), 1690 (s), 1677 (s), 1603 (m) cm^{-1}; nmr (δ): 0.13 (s, 9H), 1.53–2.15 (m, 4H), 2.35–2.70 (m, 3H), 2.77 (db of db, incompletely resolved, J = 6.3, 16.2 Hz, 1H), 3.47 (db, J = 4.5, 16.2 Hz, 1H), 7.15–7.67 (m, 3H), 7.90–8.07 (m, 1H); ms (EI): 302 (M^+). The identity of **1***a* was further established by conversion (Zn/AcOH) to the β-diketone **10**, mp 74–76°C, identical with an unambiguously synthesized sample. The ring fusion in **1***a* is shown as *cis*, as it is in the tetracyclines, for mechanistic reasons.[4] It is of some interest that the conditions which were successful with the phenyl ester **9** were unsuccessful with the corresponding methyl ester.

[3] For related reactions, see ref. 4.

[4] This is a consequence of geometric requirements for the cyclization reaction (cf. "Baldwin rules").



9 **10**

Acknowledgments

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