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Convergent Stereospecific Total Synthesis of Monocillin I and Monorden (or Radicicol)

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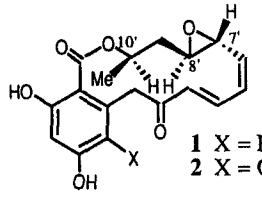
Abstract : *The first total syntheses of the antifungal resorcylic macrolides Monocillin I and Monorden (or Radicicol) have been achieved by a convergent stereospecific route.TBDMS phenol ethers were found to be suitable for all the scheme and were removed in the ultimate step under mild conditions (aqueous borax/THF/methanol), hence allowing to get the natural macrolides in good yields, with no degradation. An efficient conversion of di-OTBDMS Monocillin I into Monorden is also reported.*

The mycotoxins Monocillin I **1** [1] and Monorden (or Radicicol) **2** [1, 2] are 14 - membered resorcylic macrolides which have interesting pharmacological properties [1 - 3]. Their structures only differ by the chlorine substitution [4] and a recent X-ray study established the three asymmetric carbon atoms as having the *R* configuration [2j].



1 X = H Monocillin I
2 X = Cl Monorden (or Radicicol)

In the preceeding communication, we reported a convergent stereospecific route to di-O-methyl derivatives related to Monocillin I [5]. The same strategy might also be applied for the preparation of monochiral related unnatural macrolides. However, one remaining difficulty was to find a suitable phenol protecting group, compatible with the reaction conditions and whose removal would not affect the highly sensitive natural macrolides, such as **1** and **2** [2e].

The synthesis of Monocillin I was achieved according to Scheme 1, using the palladium-catalyzed coupling of the di O-TBDMS chloromethyl isocoumarin **5** with the monochiral vinylstannane **7** [5, 6].

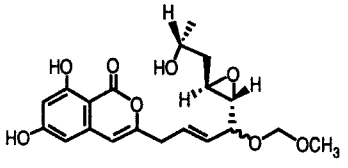
The isocoumarin **5** was obtained in 93% overall yield from **3** [5], by demethylation with boron tribromide and then silylation in standard conditions. Noteworthy, complete halogen exchange occurs in situ in the silylation step, as shown by NMR and MS. Deprotection of the silyl ether **6** [5] with nBu_4N^+, F^- afforded **7** in 98% yield. The coupling of **5** (1.0eq) with **7** (1.1eq) was done in the same conditions as previously [5] (3% mol $PdCl_2$ $(CH_3CN)_2$, 5% mol PPh_3, DME reflux, argon), for **3** and **6** [5], affording **8** in a good yield (75%).

Isocoumarin cleavage was achieved in two steps [5] to obtain the keto acid **9** in 44-55% overall isolated yield (69-78% corr.). It is worth to point out that all the keto acid produced, **9**, was specifically deprotected at the position ortho to the carboxyl group ; in contrast, the recovered isocoumarin (30-35%) was only the di O-TBDMS isocoumarin **8**, although reduction (DIBAH-THF) of **8** into the intermediate lactol was secured to be complete [7].

Under Mitsunobu reaction conditions, **9** (5.10^{-3} M in anhyd. toluene, r.tp) afforded cleanly the desired macrolide **10** in 71% isolated yield, together with 4% of cyclic 28-membered diolide NMR, FAB $(M+Na)^+$ = 1035). No isocoumarin was formed, in sharp contrast with our previous result with the di-O-methyl hydroxy keto acid which yielded the isocoumarin as the major product (20 - 35%) in the same conditions, with only 15 - 20% macrolide [5].

Attempted elimination of the OMOM group by reacting **10** with DBU (benzene reflux, argon) only led to the isocoumarin **13** (76%) whereas the di-OTBDMS derivative **11** was inert in the same conditions. This result was surprising since the same conditions applied to the di-OMe analogue yielded the desired conjugated dienone epoxide macrolide in a stereospecific and nearly quantitative reaction [5]. The desired lactone **12** was however obtained-but only in 25-30% yield - in a stereospecific reaction by heating **11** with anhydrous K_2CO_3 in DME (reflux, argon). Strikingly, two other products, **14** and **15**, were formed in a nearly 1/1 ratio and isolated (15 - 25%), probably resulting from an efficient quenching of formaldehyde (progressively generated in situ in the elimination step via the equilibrium $CH_3OCH_2O^- \rightleftharpoons HCHO+CH_3O^-$) by the two incipient regioisomeric enolates.

Monocillin I **1** was finally obtained in a nearly quantitative yield by deprotection of the phenolic TBDMS ethers under mild conditions we found (aq. borax/THF/CH_3OH, r.tp, overnight).



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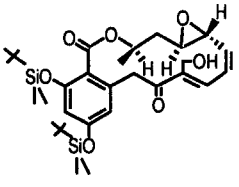

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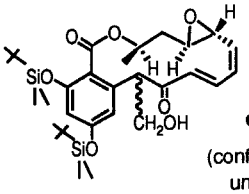

15

Only one diastereoisomer

(configuration at C-1' unknown)

Conversion of Monocillin I into Monorden (Scheme 2) has already been achieved in low yield with NCS in DMF by Ayer et al. [4]. Chlorination by calcium hypochlorite in a biphasic medium, in buffered conditions (ice-bath), proved unsatisfactory when applied to Monocillin I, but gave a very clean conversion of **12** into **16**. Deprotection of crude **16**, in the same conditions as above for **12**, was slower, yielding after 24h the specifically mono deprotected macrolide **17** and Monorden **2**, respectively in 22% and 67% isolated yield. Fortunately at 40-50°, **2** was obtained in 90% overall yield from **12**.

Unambiguous identification of the synthetic monochiral macrolides, **1** and **2**, was made with the original spectral data and a natural sample of Monorden kindly provided by Professor Ayer to whom we express our acknowledgements [8]. Further improvements of some steps of this route are currently under study.

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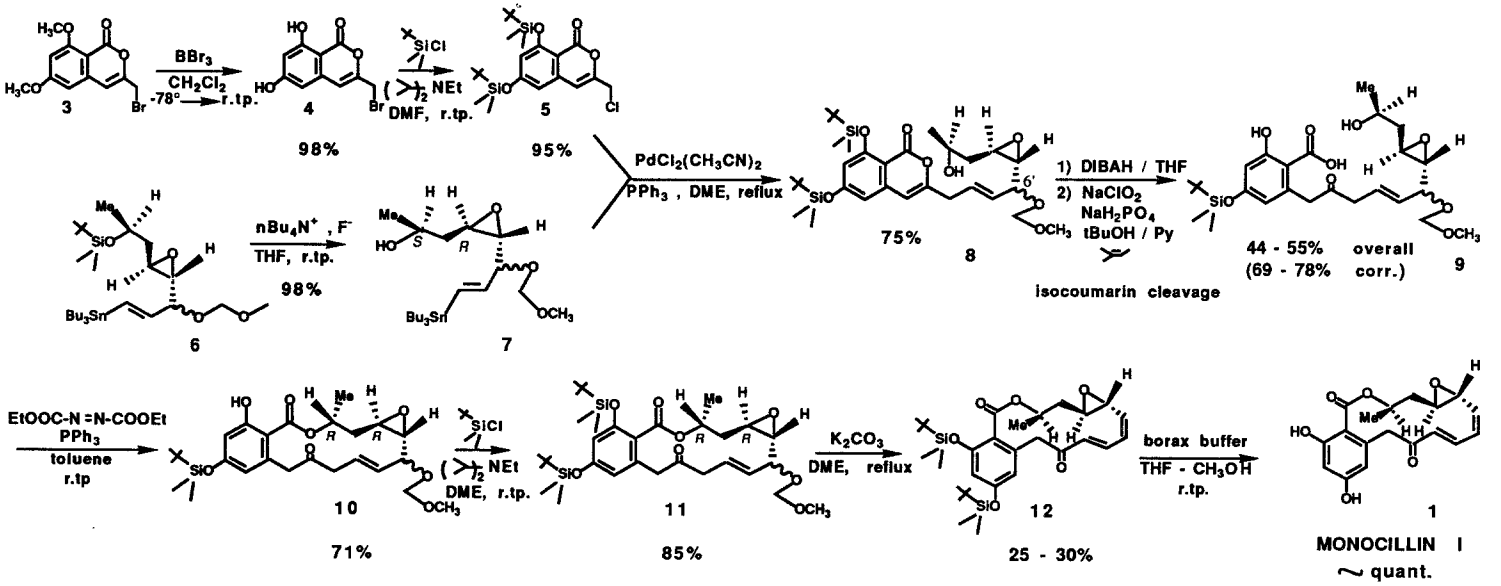
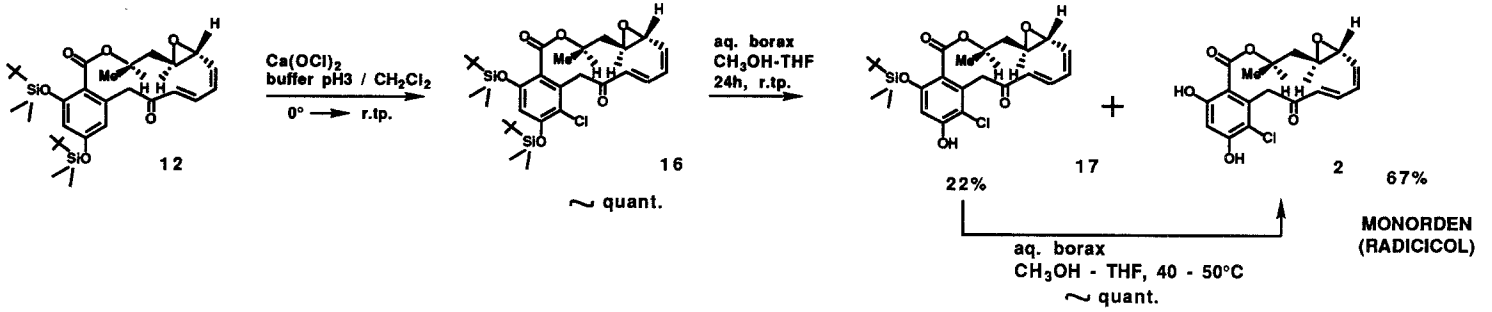
Monocillin I synthesis (Scheme 1)



Monorden synthesis (Scheme 2)



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   The isocoumarin **3** is prepared in 34 % overall yield from orcinol hydrate.
6. A pure diastereoisomer corresponding to the major condensation product of the monochiral epoxy aldehyde and *E*-tributylstannyl vinyl lithium was used throughout the complete scheme (configuration not determined at C-6').
7. Specific deprotection to yield **9** possibly occurs in the oxidation step either via an intramolecular nucleophilic attack at silicon by the carboxylate and further hydrolysis of the intermediate silyl ester, or by a general base catalysis involving the carboxylate. No migration of silyl group or desilylation occurs in the DIBAH reduction.
8. This identification also clearly demonstrates that a stereospecific inversion of configuration occurs in the Mitsunobu macrolactonisation step. No other diastereoisomeric lactone could be detected.

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