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Convergent Stereospecific Total Synthesis of Monochiral Monocillin I Related Macrolides.

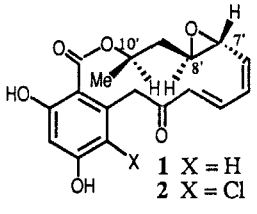
Maxime Lampilas and Robert Lett*

Unité Mixte CNRS - Roussel Uclaf (UMR 26)
BP 9 - 93230 Romainville (France)

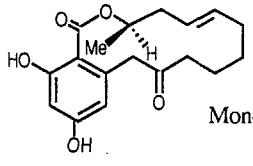
Abstract *:The first total synthesis of Monocillin I related macrolides has been achieved by a convergent and stereospecific route involving the palladium - catalyzed coupling of a functionnalized chiral vinylstannane with the appropriate dimethoxy bromomethyl isocoumarin. Cleavage conditions of the isocoumarin ring were then found for the preparation of a precursor hydroxy acid. The 14-membered macrolide was obtained in the Mitsunobu reaction conditions, and the required natural conjugated dienone epoxide system of Monocillin I was generated stereospecifically from that macrocyclic precursor.*

Tsuneda and Hiratsuka have reported that *Monocillium nordinii* is a destructive mycoparasite of pine stem rust fungi [1]. The active antifungal metabolites were isolated by Ayer et al. and identified as 14-membered resorcylic macrolides, Monocillin I **1** and Monorden (or Radicicol) **2**. These compounds were shown to be active not only against the pine stem rusts, but also against a wide variety of other fungi, including *Ceratocystis ulmi* which is the cause of Dutch elm disease. The antifungal activity of the other isolated related metabolites (Monocillins II to V) was quite negligible [2].

Monocillin I and Monorden differ only by the chlorine substitution [3]. However, the relative and absolute configurations of these macrolides were unknown and Ayer et al. tentatively assigned the *(7'S, 8'S)* configuration of the epoxide [2]. Only recently, during the course of our synthetic approach, a X-Ray study established the three asymmetric carbon atoms as having the *R* configuration [4].



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



Monocillin IV

Ayyangar et al. recently disclosed the synthesis of (±) Monocillin IV dimethyl ether [5] and we would like to here report the first total synthesis of the *(7'S, 8'S, 10'S)* enantiomer of Monocillin I dimethyl ether and those of the natural macrolides **1** and **2** in the following communication [6].

Propargyl alcohol was protected with 2-methoxy propene ($POCl_3$ I% v/v in CH_2Cl_2, r. tp.) to yield **3** (~quant. crude, 85% after distillation over anhyd. K_2CO_3). The lithio derivative of **3** was reacted with 1.0 eq

R (or *S*) propylene oxide, in anhydrous THF at -78°, in the presence of BF_3 - Et_2O [7] (slow addition of 1.0 eq) to afford after aqueous ammonia quench the condensation product **4**. The alcohol **4** was immediately silylated in the usual conditions without intermediate purification. The ketal protective group was selectively removed by stirring **4** in methanol over IRN77, at r.tp., to give **5** in 80 % overall yield from **3**. The reduction of **5** into **6** proved to be difficult and was best done using Corey conditions [8] with 1.3 eq ($AlLiH_4$, $2CH_3ONa$) in THF, in order to avoid allene formation and silyl ether cleavage. The E allylic alcohol **6** was obtained in 75-80 % yield and no Z isomer was detected (Scheme 1).

Sharpless asymmetric epoxidation of either *R* (or *S*) monochiral *E* allylic alcohol **6** gave a good stereospecific access to each enantiomerically pure diastereoisomer, either with (+) or (-) diethyl tartrate (Scheme 2) [9], the absolute and relative configurations of which were unambiguously established by chemical correlation [10] and shown to be consistent with the Sharpless asymmetric epoxidation empirical rule [11, 12].

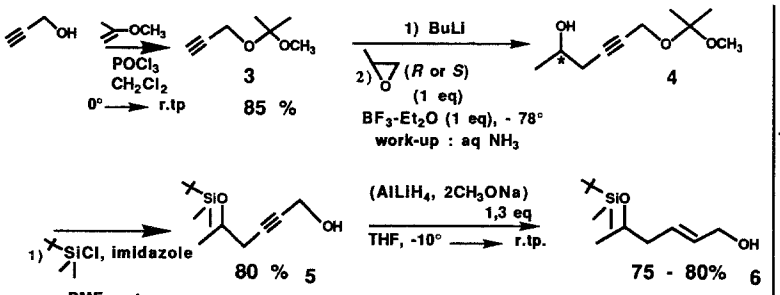
The epoxy aldehyde **8**, obtained by Swern oxidation [13] of **7** in 87-90% yield (CH_2Cl_2, 2.4 eq DMSO, 1.1 eq oxalyl chloride, -60° and then 5 eq NEt_3), was further condensed at -78° with the *E* lithio reagent **10**, prepared in situ by clean transmetallation [14] of pure E **9** [15] in THF-hexane, to afford a 75/25 mixture of diastereoisomers **11** in 55-60% yield (76-81% corr.) and 25-30% recovered pure aldehyde **8** after chromatography. The two isomers were separated and only the major one was used in the complete further sequence of Scheme 3 [16].

Our preliminary work showed that protection of the hydroxyl group was necessary to avoid side-reactions in the subsequent macrolactonisation step [10] ; therefore **11** was reacted with a preformed solution of MOM chloride [17] to give **12** in 92% yield.

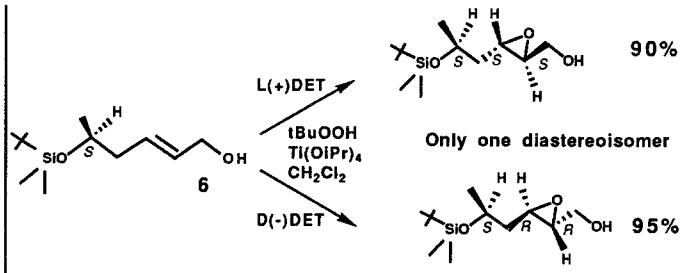
On the other hand, the brominated isocoumarin **13** was prepared in 34% overall yield from orcinol hydrate [10]. The coupling of **12** (1.06 eq) with **13** (1.0 eq), catalysed by 3% mol $PdCl_2(CH_3CN)_2$ with 5% mol PPh_3 in DME at reflux, afforded **14** in 75% yield after chromatography. Noteworthy, no cleavage of the epoxide was observed [18], in contrast with some recent results concerning nucleophilic opening of a-epoxy alcohols in similar conditions [19].

The isocoumarin cleavage could not be achieved under aqueous basic conditions (OH^- or HCO_3^-) which, even at r.tp., induced degradation and formation of numerous products. Attempted hydrolysis of **14** with 1 eq NaOH in excess H_2O_2 30% (pH 11.6) [20] only gave an allylic dimethoxy homophtalate as a regiospecific Baeyer-Villiger rearrangement product, and the corresponding sodium homophtalate [10]. The keto acid **15** was however obtained in two steps in 52-55% overall yield, with 25% recovered isocoumarin **14**. Silyl ether cleavage of **15** afforded the hydroxy acid **16** in 80% yield. The macrolactonisation of **16** turned out to be quite a difficult problem due to the largely favoured isocoumarin formation either by acyl activation or even using Mitsunobu hydroxyl group activation conditions [21, 26]. The macrolide **17** was however obtained in 15-20% yield (**16**, 2eq PPh_3, 1.4 eq DEAD, toluene, 20°), together with 20-35% isocoumarin **14** (10'-OH(*R*)) and 7% 28-membered ring cyclic diolide [27]. Macrolide **17** reacted with DBU (1eq) in benzene at reflux, under argon, to give in a nearly quantitative yield the enantiomer **18** of di-O-methyl Monocillin I, remarkably in a stereospecific reaction, thus demonstrating that macrolactonisation step had occurred with complete inversion of configuration at C-10'.

The present convergent scheme is highly flexible for the total synthesis of monochiral unnatural resorcylic macrolides for further studies.

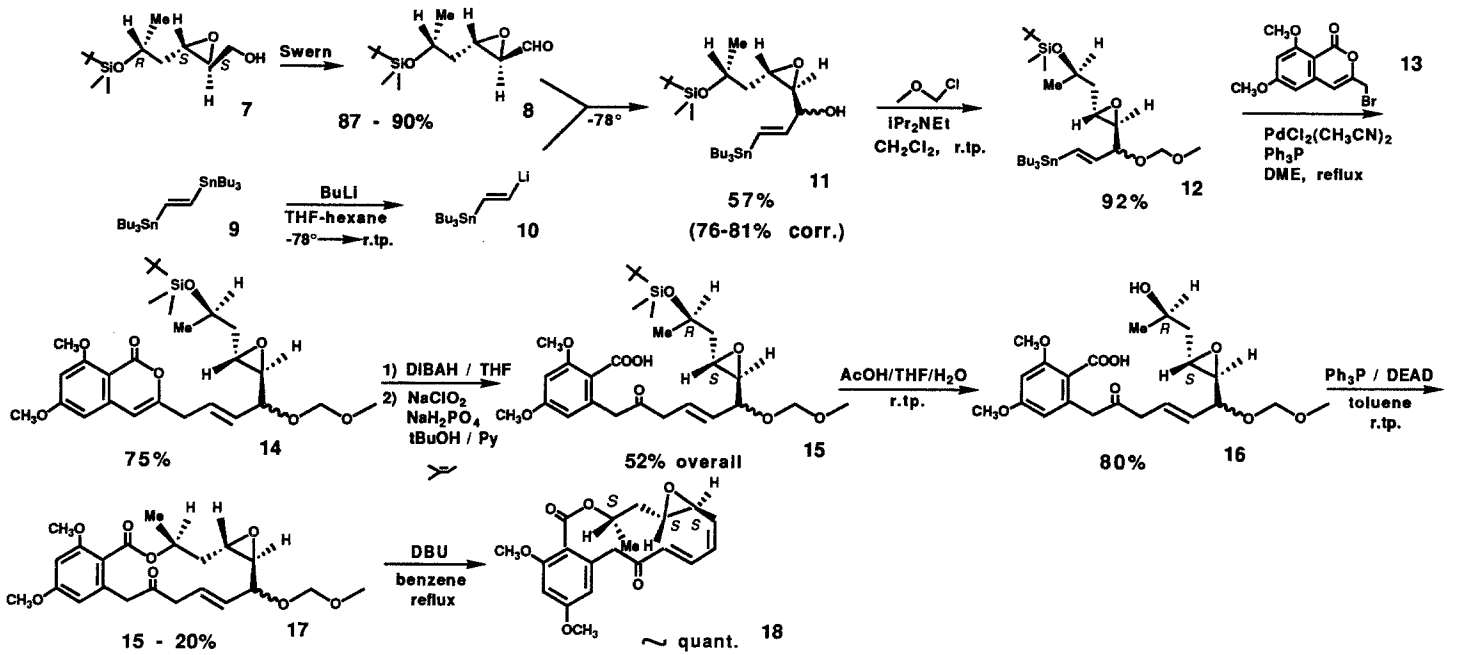


Scheme 1



Scheme 2

Scheme 3



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9. Epoxidation of (±) **6** with MCPBA (CH_2Cl_2, O°) gave a 90/10 mixture of respectively the threo and erythro epoxy alcohols. Epoxidations with tBuOOH catalyzed either by $VO(acac)_2$ or $Mo(CO)_6$, or $Ti(OiPr)_4$, gave all a 1/1 mixture of diastereoisomers as did the reaction with H_2O_2 30% catalyzed by H_2WO_4/AcONa.
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12. Noteworthy, the configuration of the formed epoxide is only determined here by the chirality of the diethyl tartrate and there is no double asymmetric induction by the chiral center of **6**. Conversely, in order to get a pure monochiral diastereoisomer **7**, it is necessary to use a monochiral allylic alcohol **6** since there is no kinetic difference inthese examples ; epoxidation of (±) **6** with L(+) DET yields a 50/50 mixture of the (*SSS*) and (*RSS*) diastereoisomers (see Scheme 2).
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16. The configuration of the allylic alcohol, at C-6', was not determined.
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21. Attempted macrolactonisation of the (10'*R*, 8'*R*) diastereoisomer of **16** using various procedures (DCC/DMAP [22] , Corey-Nicolaou [23], Mukaiyama [24], Yamaguchi [25]) only led to isocoumarin formation. Protection of the carbonyl group as N-dimethyl hydrazone or O-methyl oxime did not prevent the six membered ring formation [10].
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27. The same Mitsunobu reaction conditions, but in CH_2Cl_2 or THF, only gave the isocoumarin **14** (10'-OH(*R*)) [10]. Noteworthy, isocoumarin formation in the Mitsunobu reaction conditions must involve an acyl activation, possibly via a triphenyl alkoxy acyloxy phosphorane. We observed that the Mitsunobu macrolactonisation is greatly improved (71%) if the precursor hydroxy acid has a free phenol ortho to the carboxyl group [6, 10].

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