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Convergent stereospecific total synthesis of monocillin I and radicicol: some simplifications and improvements

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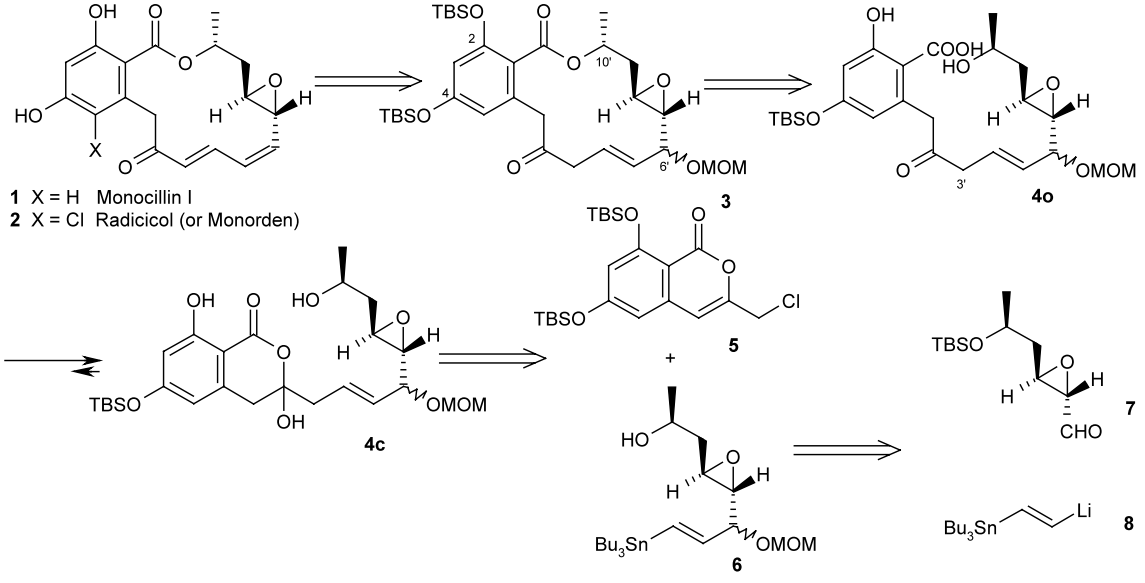
Abstract—A much improved and reliable access to the macrolide **9**, key-intermediate in our synthesis of monocillin I and radicicol is reported, via a modification of our first synthesis. The formation of the conjugated *E*,*Z*-dienone *trans*-epoxide is now achieved in a much higher yield, in a stereospecific reaction, by elimination of the methanesulfonate ester of the 6′-OH of the intermediate macrolide. It is also shown that the configuration of the 6′-OH has no significant incidence on all the steps leading to **9**, and that consequently the two diastereoisomers **12**, epimeric at 6′, can be used for the synthesis of radicicol.

The recent publication[1] of a new asymmetric synthesis of monocillin I **1** and radicicol **2** by Danishefsky and co-workers prompts us now to disclose some improvements and simplifications of our first synthesis of these molecules.[2]

Our original synthetic approach was achieved according to Scheme 1. A difficult step in our synthesis was the generation of the conjugated dienone epoxide from the macrolide **3**. Our previous results showed it was necessary to protect the 6′-OH, in order to be able to



Scheme 1.

Keywords: macrolides; isocoumarins; tin and compounds; coupling reactions; dienones; Mitsunobu reactions.

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achieve the macrolactonization, in Mitsunobu reaction conditions, of the intermediate keto hydroxy acid **4o** which moreover exists in solution in the quasi-unique hemiketal closed form **4c** as shown by NMR (200 or 400 MHz, $CDCl_3$, rt) and IR ($CHCl_3$).[2d,3] Therefore, our first synthesis was completed with the 6′-OMOM protected derivatives, since the protection of the 6′-OH was very efficient with a preformed MOMCl solution and the $MOMO^-$ anion could also be envisaged as a reasonable leaving group, this in our initial approach for the generation of the conjugated dienone epoxide to obtain **9** from the macrolide **3**, in necessarily sufficiently mild basic and nonnucleophilic conditions in order to be able to preserve the structures.

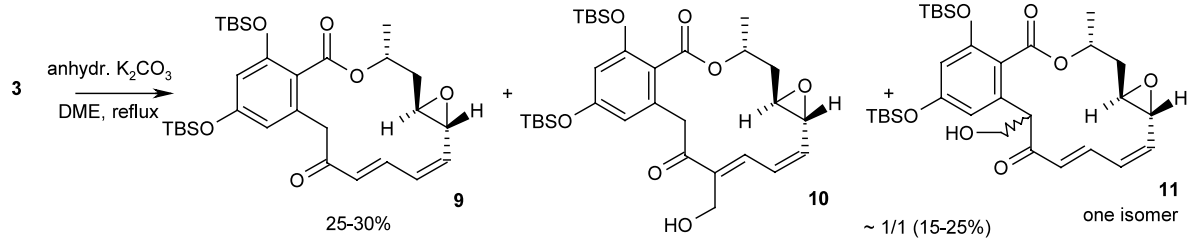
However, if the desired macrolide **9** could be obtained in a stereospecific reaction from **3**, it was only in a 25–30% yield, by using anhydrous K_2CO_3 (1.3 equiv.) (DME, reflux, 1 h); quite surprisingly, two other macrolides **10** and **11** were also isolated in 15–25% yield (in a ca. 1/1 ratio), resulting from the quench by each regioisomeric enolate of the anhydrous formaldehyde generated in situ by the elimination of the OMOM ether, via the equilibrium between $CH_3OCH_2O^-$ and HCHO plus CH_3O^- (Scheme 2).[2] To our knowledge, such a reaction has only been previously reported in a fragmentation–recombination reaction of methoxymethylester enolates.[4] Elimination of $MOMO^-$ most likely is not concerted to give free formaldehyde and CH_3O^-, the equilibrium being highly shifted towards $CH_3OCH_2O^-$ in the reaction conditions.[5] Consistently, in order to avoid the hydroxymethylation reaction, attempted elimination of the 6′-OMe derivative in the same anhydrous conditions (K_2CO_3, DME, reflux) only led to degradation products, due to the greater basicity of CH_3O^-, thus showing that the MOM ether had a very subtle role in the elimination reaction.[2d,3]

Further improvements were clearly necessary for the generation of the conjugated dienone epoxide in order to obtain **9** in a higher yield, via a reliable reproducible reaction. The problem was here that a good leaving group could not be introduced early in the sequence and, therefore, we had to find a suitable protective group of the 6′-OH, allowing its efficient deprotection after the macrolactonization in order to obtain the macrolide 6′-OH **19** in high yield. Consequently, a sequence was developed, based on the protection of the 6′-OH as an OMPM ether immediately after the condensation of the enantiomerically pure epoxyaldehyde **7** with the *E* tributylstannylvinyllithio derivative **8** (Scheme 3).[3]

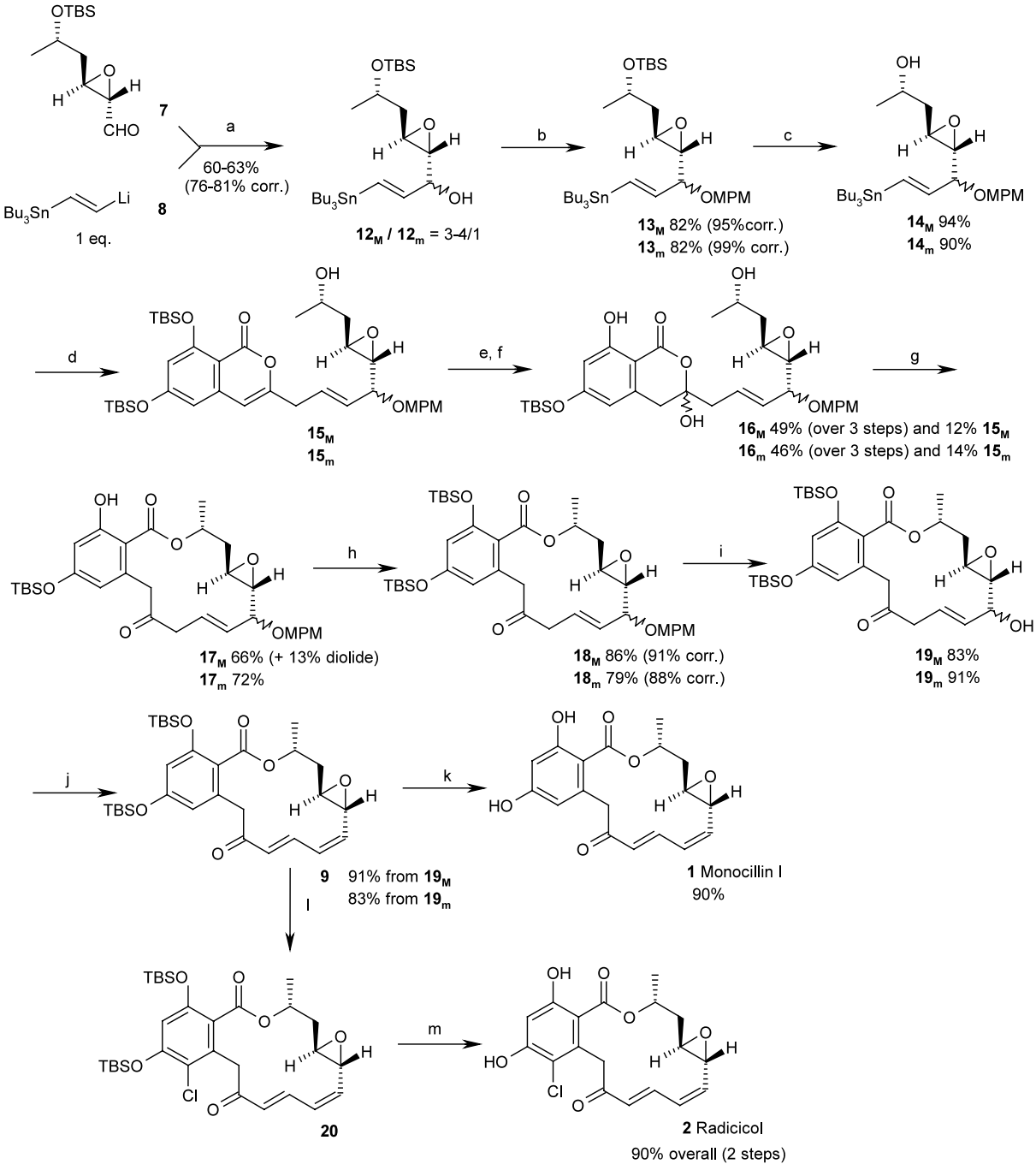
On the other hand, that condensation afforded a 3-4/1 mixture of the two diastereoisomers $\mathbf{12_M}$ (major adduct) and $\mathbf{12_m}$ (minor adduct), epimeric at 6′ and in a first approach the completion of our synthesis was initially achieved only with **6** as the major diastereoisomer (configuration at C-6′ not determined), obtained pure after chromatography over silica gel.[2] Therefore, it was now of some interest to examine the further steps of the sequence with the minor diastereoisomer in order to see if it could be also used successfully for the synthesis of monocillin I and radicicol or, if not, it was then necessary to improve the stereoselectivity of the condensation between **7** and **8** or to invert the configuration of the minor adduct.

Starting the sequence from the minor adduct $\mathbf{12_m}$, it was of particular relevance to examine the macrolactonization step in Mitsunobu reaction conditions, and also the formation of the conjugated dienone epoxide to get the macrolide **9**. Those two steps might indeed be dependent on the conformation of the acyclic precursor ($\mathbf{16_M}$, $\mathbf{16_m}$) or on the conformational constraints of the formed macrolide ($\mathbf{17_M}$, $\mathbf{17_m}$) concerning the macrolactonization step, or on the conformation of the 6′-OMs macrolide derivative (from $\mathbf{19_M}$ or $\mathbf{19_m}$) for the elimination affording **9**, conformations which may be different for the two epimers at 6′ due to the established influence of the 6′-OR substituent configuration for determining the privileged conformation of the macrocycle of resorcylic macrolides.[6] In this same communication, we wish also now to report that the two diastereoisomeric adducts $\mathbf{12_M}$ and $\mathbf{12_m}$, epimeric at C-6′, can be employed in our synthesis of monocillin I and radicicol, the configuration at C-6′ having no real significant incidence on each individual step of the sequence, and quite unexpectedly on particularly the two aforementioned key-steps (Scheme 3).[3] Consequently, these two diastereoisomers do not need to be separated and the whole sequence (**12** to **9**) can now be achieved on the mixture of epimers at C-6′.

Starting from the adduct $\mathbf{12_M}$ or $\mathbf{12_m}$, the protection of the 6′-OH by MPMCl (1.5 equiv.) required the formation of the lithium alkoxide and HMPA as a cosolvent (THF/hexane/HMPA 1/1/1, rt, 48 h) to yield $\mathbf{13_M}$ or $\mathbf{13_m}$ in 82% yield, and some starting material (15–17%) was still recovered after chromatography in each case. Deprotection of the silyl ether (TBAF/THF, rt)



Scheme 2.



Scheme 3. *Reagents and conditions*: (a) **8** from *E*-1,2-bistributylstannylethylene (1.0 equiv.) and *n*BuLi (1.0 equiv.) in THF–hexane (4/1), rt, 10 min, then **7** (1.0 equiv.) in THF at −78°C, 40 min, NH_4Cl quench; (b) BuLi (1.0 equiv.)/THF–hexane (1/1), −78°C, then MPMCl (1.5 equiv.), HMPA, 48 h, rt; (c) TBAF 1 M in THF (3 equiv.), rt, overnight; (d) **5** (0.97 equiv.), 3 mol% $PdCl_2(CH_3CN)_2$, 5 mol% PPh_3, DME, reflux, 2 h 30 min; (e) DIBAH (10 equiv.), THF–hexane (2/1), −78°C, 45 min, then acetone quench and pH 4 buffer; (f) crude product in *t*BuOH/H_2O/2-methyl 2-butene (1/1/1) $NaClO_2 \cdot H_2O$ (7 equiv.), $NaH_2PO_4 \cdot 2H_2O$ (18 equiv.), pyridine (6 equiv.), 5 days, rt, pH 3 work-up; (g) **16** (0.005 M) in toluene, PPh_3 (2 equiv.), then DEAD (1.4 equiv.), rt, 1 h; (h) TBSCl/*i*Pr_2NEt (1.6 equiv.), DMF, rt, 3 h, then pH 3 buffer work-up; (i) DDQ (2.5 equiv.), CH_2Cl_2–H_2O (9/1), rt, 1 h; (j) CH_3SO_2Cl (1.5 equiv.), NEt_3 (3.25 equiv.), CH_2Cl_2, 0°C; (k) borax buffer/MeOH (1/1), rt, 24 h, then pH 3 buffer work-up; (l) **9** (0.004 M) in CH_2Cl_2/pH 3 buffer (2/1), 0°C, then addition of $Ca(OCl)_2$ 0.038 M in H_2O until no more starting material (followed by TLC); (m) crude **20** in THF/MeOH/borax buffer (1/1/1), 40–50°C, 8 h, then pH 3 buffer work-up.

afforded $\mathbf{14_M}$ or $\mathbf{14_m}$ in high yield. Subsequent coupling with the chloromethyl-isocoumarin **5** (0.97 equiv.), catalyzed by 3 mol% $PdCl_2(CH_3CN)_2$ with 5 mol% PPh_3 (DME, reflux) afforded $\mathbf{15_M}$ or $\mathbf{15_m}$ in ca. 75% yield after chromatography.

For related compounds, we previously observed that the isocoumarin cleavage could not be achieved in aqueous basic conditions, even at room temperature, since they led immediately only to degradation and complex mixtures and that NaOH (1.4 equiv.) in excess

30% H_2O_2 did also not afford the desired keto-acid.[2] Therefore, the isocoumarin cleavage was achieved as previously in two steps to obtain the keto-acid in the quasi-unique hemiketal form $\mathbf{16_M}$ (or $\mathbf{16_m}$) in solution (as shown by NMR) in 46–49% overall yield for the three steps (d, e, f), and 12–14% of the bis-OTBS isocoumarin $\mathbf{15_M}$ (or $\mathbf{15_m}$) were also reisolated after chromatography. It is worth to point out that, for the DIBAH reduction, quench with excess acetone at −78°C followed by pH 4 work-up for extraction is crucial in order to get cleanly the lactol; at pH 3, other products were formed and at pH above 7 a naphthol is exclusively formed via an intramolecular aldol of the keto-aldehyde open form. The equilibrium between the lactol and the keto-aldehyde can be induced by the addition of pyridine (6 equiv.), with no naphthol formation, in order to allow the oxidation of the aldehyde into a carboxylic acid by $NaClO_2$ in buffered conditions.[2] It is also worth emphasizing that the reduction of $\mathbf{15_M}$ (or $\mathbf{15_m}$) was complete and that no appreciable desilylation occurred during the reduction, as shown by the NMR of the crude product.[3] On the other hand, the specific deprotection of the phenol at the *ortho* position which is observed in obtaining $\mathbf{16_M}$ (or $\mathbf{16_m}$) is most likely the result of an intramolecular silyl group migration involving the intermediate carboxylate anion which is formed in the oxidation step, and subsequent hydrolysis of the silyl ester. That specific deprotection is quite fortunate, since we showed earlier that the free *ortho*-phenol had a determining effect for favoring the macrolactonization with respect to the competitive isocoumarin formation.[2] Under Mitsunobu reaction conditions ($\mathbf{16_M}$ or $\mathbf{16_m}$ 5×10^{-3} M in anhydr. toluene, rt), the macrolides $\mathbf{17_M}$ and $\mathbf{17_m}$ were isolated in 66 and 72% yield, respectively, after chromatography. These macrolactonizations appear to be quite unique, since being achieved from a precursor which is not a free hydroxy acid, but which is under the quasi-exclusive cyclic hemiketal form in solution, they are also unique with respect to the severe competition between the 14-membered macrolide and the isocoumarin formations. At this stage, however, the *o*-phenol had to be reprotected as an OTBS ether since our previous work showed it was necessary not to have a free *o*-phenol, which led only to reformation of the isocoumarin during the attempted elimination of the OMOM ether followed by subsequent degradation.[2] That protection had to be carried out in conditions avoiding enolization of the ketone at 2′, which could be achieved by TBSCl/iPr$_2$NEt in DMF at rt, to produce $\mathbf{18_M}$ and $\mathbf{18_m}$ in good yield. Subsequent deprotection of the 6′-OMPM ether[7] was efficient with DDQ in CH_2Cl_2–H_2O (9/1) (rt, 1 h) to afford $\mathbf{19_M}$ and $\mathbf{19_m}$ (83 and 91% yield, respectively). The 6′-OMs derivative was then formed (CH_3SO_2Cl/NEt_3, CH_2Cl_2, 0°C to rt) and its elimination occurred in situ, as soon as formed, in the presence of an excess of amine in very mild conditions, in a clean stereospecific reaction affording only the desired macrolide **9** in high yield (91% from $\mathbf{19_M}$, 83% from $\mathbf{19_m}$). The new sequence[3] described herein gives thus a much improved and reliable access to the key-macrolide **9**, and consequently to monocillin I and radicicol, as already described in our initial approach.[2] Our synthesis is convergent, stereospecific, yielding enantiomerically pure compounds, and is quite flexible for producing related unnatural macrolides. In order to further illustrate that flexibility, the macrolides **23** and **24** were obtained from the major adduct $\mathbf{21_M}$, via the key-macrolide **22**. It is worth pointing out that the diastereoisomeric *trans* epoxide here results in very different steric and conformational constraints and that, quite remarkably, the sequence could be achieved in quite comparable yields (Scheme 4).[3] In the accompanying communication, we also describe other improvements of our synthesis by a modification via palladium-catalyzed vinyldisiamylboranes couplings with the chloromethylisocoumarin **5**.[8]

Acknowledgements

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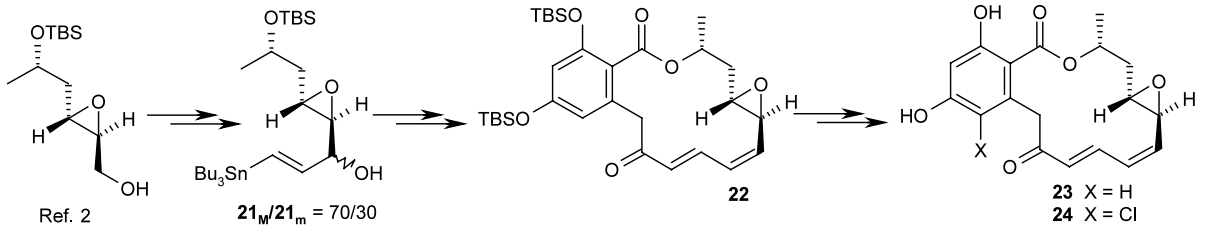

Scheme 4. *Reagents and conditions*: as for Scheme 3. (a) 55% (74% corr.); (b) 80% (90% corr.); (c) 94%; (d, e, f) 54% overall (three steps); (g) 62%; (h) 85%; (i) 91%; (j) 90%; (k) 91%; (l) and (m) (48 h, rt) 47% overall (two steps).

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