

Magali Defosseux, Nicolas Blanchard, Christophe Meyer,\* and Janine Cossy\*

*christophe.meyer@espci.fr; janine.cossy@espci.fr*

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Many naturally occurring polyoxygenated ionophores exhibit useful antiinfectious properties due to their capacity to form lipophilic complexes with various cations, which affects proton-cation exchange processes across biological membranes.<sup>1,2</sup> In 1984, two independent reports described the isolation of apparently the same new monocarboxylic acid ionophore antibiotic from strains of *Streptomyces griseus*, which on the basis of its exceptional high affinity for divalent cations and especially zinc was given the trivial name zincophorin (Scheme 1).<sup>3,4</sup> Zincophorin exhibits good in vitro activity against Gram-positive bacteria,<sup>3,4</sup> and its methyl ester also possesses antiviral activity, with reduced host cell toxicity compared to the free acid.<sup>5</sup> Although the preparation of elaborated fragments of zincophorin has been reported,<sup>6-8</sup> to date, only a single total synthesis has been completed by

With the aim of performing a convergent synthesis of zincophorin, a challenging goal involved the disconnection of the carbon framework within the C9–C13 stereopentad segment. As *anti,anti*-methyl-hydroxyl-methyl arrays have

Chemical reaction scheme showing the synthesis of (S)-ethyl lactate from zincophorin (1).

Starting material: **1** (zincophorin, R = H).  
 Reagent: R = Me.  
 Intermediate: **2** (R = Me).  
 Reagent: Alkyne reduction.  
 Intermediate: **3** (alkyne intermediate).  
 Reagent: [3,3]-sigmatropic rearrangement.  
 Intermediate: **4** (P = TBS, TBS = *t*BuMe<sub>2</sub>Si).  
 Reagent: P = TBS = *t*BuMe<sub>2</sub>Si.  
 Intermediate: **5** (alkyne intermediate).  
 Reagent: (S)-Ethyl lactate.  
 Final product: (S)-Ethyl lactate.

(5) (a) Gräfe, U.; Tonew, E.; Schade, W.; Reinhardt, G.; Härtl, A. Ger. (East) Patent DD 231 793, 1986. (b) Tonew, E.; Tonew, M.; Gräfe, U.; Zopel, P. *Pharmazie* **1988**, *43*, 717.

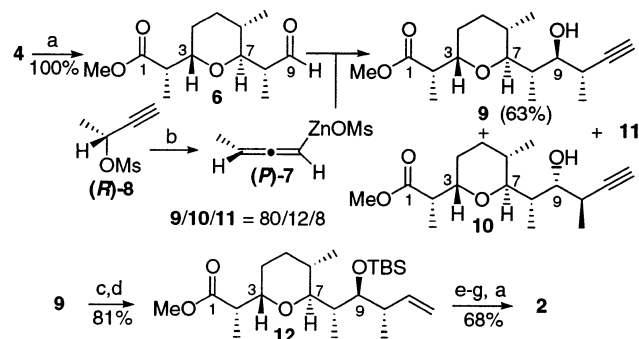
been recognized to be the most difficult to synthesize,<sup>9</sup> a plausible disconnection was the C12–C13 bond, and in the forward sense, its construction was envisaged by performing an aldol condensation between the (*Z*)-enolate derived from ethyl ketone **2** and aldehyde **3**. The ethyl ketone **2** could be prepared by an appropriate stereoselective chain extension of alcohol **4** incorporating the C1–C9 subunit of zincophorin.<sup>8</sup> On the other hand, the synthesis of aldehyde **3** was envisaged from the homopropargylic alcohol **5**, possessing the C18 and C19 stereocenters of zincophorin, which can be prepared from (*S*)-ethyl lactate.<sup>10</sup> Our synthetic plan for aldehyde **3** relied on the introduction of the C13–C15 three-carbon unit by alkylation of the terminal alkyne moiety in **5**, a stereoselective reduction of the triple bond for the elaboration of the C16–C17 disubstituted (*E*)-alkene, and a [3,3]-sigmatropic rearrangement for the creation of the C20–C21 (*E*)-trisubstituted alkene, as well as the installation of the C22 stereocenter with the requisite configuration (Scheme 1).

An efficient synthetic approach toward the C1–C9 subunit **4** has already been reported, in which an intramolecular oxymercuration of a cyclopropanemethanol was used as a key step for the elaboration of the oxygen heterocycle.<sup>8</sup> The transformation of alcohol **4** to ethyl ketone **2** was therefore investigated and required the installation of two new stereocenters (C9 and C10), which was considered to be a challenging task due to the *anti,anti* relative configuration of the C8–C10 stereotriad.<sup>9</sup>

Oxidation of alcohol **4** with Dess–Martin periodinane (DMP) afforded aldehyde **6** (100%), and the requisite C8–C9 *anti* relative configuration suggested that the chain extension using aldol, crotylmetal (or related reagents) additions to aldehyde **6** had to involve a disfavored *anti* Felkin–Anh transition state.<sup>7h,9,11</sup> Among the reagents surveyed, the chiral allenylzinc (*P*)-**7** generated from the mesylate (*R*)-**8** of (*R*)-but-3-yn-2-ol was one of the most efficient for this purpose.<sup>12</sup> However the double asymmetric condensation of (*P*)-**7** with aldehyde **6**, occurring in the mismatched manifold, afforded a diastereomeric mixture of three homopropargylic alcohols **9**, **10**, and **11** in a 80/12/8 ratio (Scheme 2).

The major diastereomer **9**, which possesses the requisite *anti,anti* relative configuration at C8–C10, was easily separated and isolated in 63% yield.<sup>13–15</sup> The synthesis of the C1–C12 subunit of zincophorin was then pursued from

**Scheme 2.** Synthesis of the C1–C12 Subunit of Zincophorin<sup>a</sup>



<sup>a</sup> Reagents and conditions: (a) DMP, pyr, CH<sub>2</sub>Cl<sub>2</sub>; (b) (*R*)-**8**, cat. Pd(OAc)<sub>2</sub>, PPh<sub>3</sub>, Et<sub>2</sub>Zn, THF, –30 °C; (c) H<sub>2</sub>, cat. Pd/BaSO<sub>4</sub>, quinoline, toluene; (d) TBSOTf, 2,6-lutidine, CH<sub>2</sub>Cl<sub>2</sub>, –78 °C; (e) cat. OsO<sub>4</sub>, NMO, acetone–H<sub>2</sub>O; (f) NaIO<sub>4</sub>, THF–H<sub>2</sub>O; (g) Et<sub>2</sub>CuLi, Et<sub>2</sub>O, –78 °C.

the homopropargylic alcohol **9**, with the partial hydrogenation of the triple bond and the protection of the hydroxyl group at C9 as a TBS ether to afford **12** (81%). This compound was transformed to ethyl ketone **2** by using a four-step sequence (68% overall yield) involving the dihydroxylation of the double bond, the oxidative cleavage of the resulting 1,2-diol to the corresponding aldehyde, the addition of excess lithium diethylcuprate, and subsequent oxidation of the secondary alcohol (Schemes 1 and 2).

Having successfully completed the synthesis of the C1–C12 subunit **2**, we next investigated the preparation of the C13–C25 subunit **3**. The homopropargylic alcohol **5** was easily accessible by addition of the chiral allenylzinc reagent (*M*)-**7** derived from the propargylic mesylate (*S*)-**8** to aldehyde **13** (derived from (*S*)-ethyl lactate).<sup>10</sup> Protection of the hydroxyl group of **5** as a MOM ether and alkylation of the terminal alkyne with the benzyl ether of 3-bromopropanol afforded the disubstituted alkyne **14** (86%). Deprotection of the TBS protecting group and oxidation of the resulting secondary alcohol with DMP gave the methyl ketone **15**

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(13) Structural assignment of the minor diastereomer **10** was supported by the fact that this compound was the only diastereomer generated (*dr* > 96/4) when the enantiomeric chiral allenylzinc (*M*)-**7** derived from the mesylate (*S*)-**8** was used as the nucleophile in the double-asymmetric condensation with aldehyde **6**, which occurs in the matched manifold. The formation of **10** therefore arose from a partial racemization of the allenylmetal reagent during the condensation with aldehyde **6**.

(14) Condensation of aldehyde **6** with the chiral (*E*)-crotylcyclopentadienyl-[(4*R*,5*R*)-2,2-dimethyl-1,3-dioxolane-4,5-diphenylmethanolato]titanium reagent<sup>15</sup> also occurred in the mismatched manifold and afforded a 70/30 diastereomeric mixture of two homoallylic alcohols of *anti* relative configuration at C9–C10 (52%). These two compounds were also respectively obtained by partial hydrogenation of the homopropargylic alcohols **9** and **10**, respectively, thereby supporting their stereochemical assignment. The relative configuration of the C8–C10 stereotriad in the third minor diastereomer **11** was anticipated to be *syn, syn*, although this was not unambiguously established. Indeed, *syn* homopropargylic alcohols are obtained as minor diastereomers in allenylzinc additions to aldehydes.<sup>12</sup> Addition of the chiral allenylzinc (*P*)-**7** to aldehyde **6** according to a Felkin–Anh transition state (substrate control) could explain the formation of **11**.

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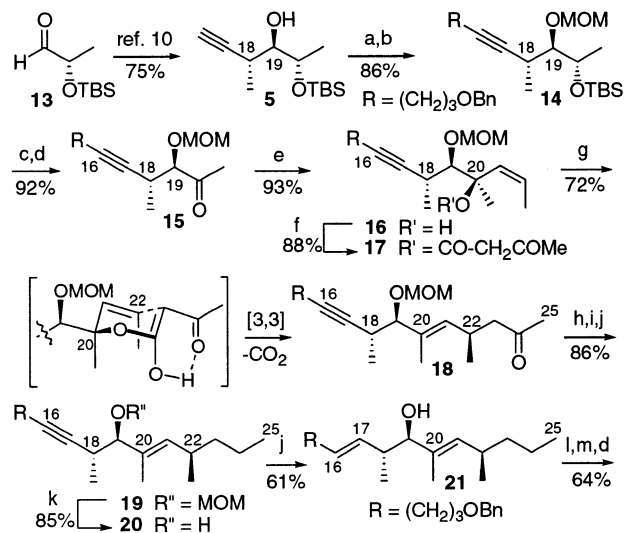
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(92%). The Cram-chelated addition<sup>11</sup> of (Z)-prop-1-enylmagnesium bromide to ketone **15** afforded the tertiary alcohol **16** (93%, 9/1 diastereomeric mixture at C20).

Whereas this hindered tertiary alcohol failed to be acetylated under a variety of conditions, ruling out the possibility of performing a subsequent Ireland–Claisen rearrangement,<sup>16</sup> reaction with diketene in the presence of a catalytic amount of DMAP proceeded smoothly to afford the  $\beta$ -ketoester **17** (88%), and the diastereomers at C20 were easily separated at this stage. This result led us to investigate the possible use of the Carroll version of the [3,3]-Claisen sigmatropic rearrangement<sup>16,17</sup> in order to perform the carbon chain extension and control the configurations of the C22 stereocenter and the C20–C21 trisubstituted alkene. Among the different reaction conditions tested, only the adsorption of the  $\beta$ -ketoester **17** on neutral alumina, followed by heating at 60 °C,<sup>18</sup> was successful at promoting the Carroll–Claisen rearrangement of **17** and afforded the unsaturated ketone **18** (72%) with high stereoselectivity ( $E/Z$  = 96/4, geometric isomers easily separated) and complete chirality transfer at C22 (Scheme 3).<sup>19,20</sup>

**Scheme 3.** Synthesis of the C13–C25 Subunit of Zincophorin<sup>a</sup>



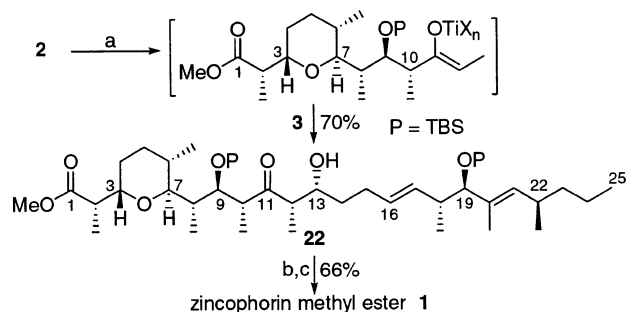
<sup>a</sup> Reagents and conditions: (a) MOMCl, *i*-Pr<sub>2</sub>NEt, CH<sub>2</sub>Cl<sub>2</sub>; (b) *n*-BuLi, THF, -78 °C then RBr, HMPA, -78 °C to room temperature; (c) TBAF, THF; (d) DMP, pyr, CH<sub>2</sub>Cl<sub>2</sub>; (e) (Z)-prop-1-enylMgBr, MgBr<sub>2</sub>·OEt<sub>2</sub>, Et<sub>2</sub>O-THF, -78 °C; (f) diketene, cat. DMAP, THF; (g) neutral Al<sub>2</sub>O<sub>3</sub>, 60 °C; (h) DIBAL-H, Et<sub>2</sub>O, -78 °C; (i) MsCl, *i*-Pr<sub>2</sub>NEt, CH<sub>2</sub>Cl<sub>2</sub>, 0 °C; (j) LiAlH<sub>4</sub>, THF, reflux; (k) *p*-TsOH, MeOH; (l) TBSOTf, 2,6-lutidine, CH<sub>2</sub>Cl<sub>2</sub>, -78 °C; (m) Li, liq. NH<sub>3</sub>, THF-*t*-BuOH, -78 °C. R = (CH<sub>2</sub>)<sub>3</sub>OBn.

The removal of the carbonyl group at C24 was accomplished by reducing ketone **18** to the secondary alcohol, formation of the mesylate, and subsequent reduction with LiAlH<sub>4</sub> to give compound **19** (86%). Since the deprotection of the hydroxyl group at C19 later in the synthesis turned out to be difficult, the troublesome methoxymethyl protecting group was cleanly cleaved at this stage (*p*-TsOH, MeOH,

rt) to produce the corresponding alcohol **20** (85%). Due to the presence of a homopropargylic hydroxyl group at C19, the triple bond in **20** was slowly but efficiently hydroaluminated with  $\text{LiAlH}_4$  in refluxing THF to elaborate the (*E*)-disubstituted C16–C17 double bond of compound **21** (61%). The hydroxyl group at C19 was reprotected as a TBS ether and the benzyl protecting group at C13 was removed by a Birch reduction. The primary alcohol was subsequently oxidized with DMP, thereby affording aldehyde **3** (64%) and concluding the synthesis of the C13–C25 subunit (Schemes 1 and 3).

The coupling of ethyl ketone **2** and aldehyde **3** was next attempted (Scheme 4).

**Scheme 4.** Total Synthesis of Zincophorin Methyl Ester<sup>a</sup>



<sup>a</sup> Reagents and conditions: (a)  $\text{TiCl}_4$ ,  $i\text{-Pr}_2\text{NEt}$ ,  $\text{CH}_2\text{Cl}_2$ ,  $-78^\circ\text{C}$ , then add **3**,  $-78^\circ\text{C}$ ; (b)  $\text{NaBH}_4$ ,  $\text{MeOH}$ ,  $0^\circ\text{C}$ ; (c)  $\text{HF}\cdot\text{pyr}$ ,  $\text{THF}$ .

On the basis of literature precedents, the stereochemical outcome of the aldol condensation between the (*Z*)-titanium enolate<sup>21</sup> of **2** and aldehyde **3** lacking  $\alpha$  and  $\beta$  stereocenters was anticipated to be exclusively controlled by the configuration of the methyl-substituted C10 stereocenter.<sup>22</sup> Accordingly, the (*Z*)-titanium enolate of ethyl ketone **2** was

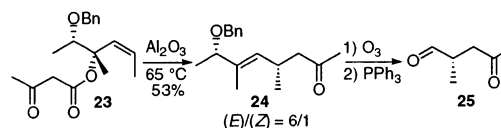
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(19) This result could be explained on the basis of the well-established preference for the [3,3]-sigmatropic rearrangements to proceed through a chairlike transition state (acyclic series),<sup>16</sup> in which the bulkier branched carbon chain, rather than the methyl group, should preferentially occupy the less congested equatorial position (Scheme 3).

(20) Carroll rearrangement of the related tertiary allylic  $\beta$ -ketoester **23**, which affords ketone **24** as the major stereomer, has also been studied as a model. Ozonolysis of **24** led to the known (*S*)-keto aldehyde **25** (unpublished results).



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generated in the standard manner<sup>21,22</sup> and its condensation with aldehyde **3** afforded aldol **22** (70%) with high diastereoselectivity (*dr* > 96/4). The diastereoselective reduction of the carbonyl group in compound **22** could be conveniently carried out by simply using NaBH<sub>4</sub> in methanol, and subsequent final cleavage of the TBS protecting groups of the alcohol moieties at C9 and C19 afforded zincophorin methyl ester **1** (66% yield from **22**), whose analytical and spectroscopic data such as *R<sub>f</sub>* in two solvent systems,<sup>5</sup> IR,<sup>5,6</sup> <sup>1</sup>H NMR spectra,<sup>6</sup> and [ $\alpha$ ]<sub>D</sub> +21.3 (*c* 0.4, CHCl<sub>3</sub>) were in perfect agreement with those previously reported in the literature ([ $\alpha$ ]<sub>D</sub> +22.4 (*c* 0.89, CHCl<sub>3</sub>);<sup>6</sup> authentic sample, [ $\alpha$ ]<sub>D</sub> +20.9 (*c* 2.0, CHCl<sub>3</sub>)<sup>1,6</sup>). Although zincophorin could be in principle generated from its methylester by saponification, characterization of the metal salt-free acid was claimed to be difficult and this compound was therefore treated with CH<sub>2</sub>N<sub>2</sub> to afford **1**.<sup>6</sup>

In conclusion, we have reported a convergent total synthesis of zincophorin methyl ester relying on a diastereoselective titanium-mediated aldol coupling between the C1–C12 and C13–C25 subunits. The latter fragment was prepared by a stereoselective Carroll–Claisen rearrangement

of a tertiary allylic  $\beta$ -ketoester, and a chain extension of the previously synthesized C1–C9 fragment<sup>8</sup> was performed by using an allenylzinc-aldehyde condensation to produce the C1–C12 fragment. Moreover, the synthetic plan used for the elaboration of the C13–C25 subunit (intermediacy of ketone **18**) should also enable access to the antibiotic CP-78,545, the related C24–C25 unsaturated analogue of zincophorin.<sup>23</sup>

**Acknowledgment.** M.D. and N.B. thank the MRES for a grant.

**Supporting Information Available:** Characterization data for compounds **1–3**, **9**, **18**, and **22**, experimental procedures for the synthesis of compounds **1** and **22**, and copies of the NMR spectra of **1**. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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