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Total synthesis of zincophorin*

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Abstract: A total synthesis of the naturally occurring ionophore zincophorin has been realized. The key steps are an intramolecular oxymercuration of a cyclopropanemethanol for the elaboration of the tetrahydropyran ring and a Carroll–Claisen rearrangement to control the configuration of the double bond at C20–C21 as well as the stereogenic center at C21.

Keywords: ionophore; zincophorin; oxymercuration; Carroll–Claisen rearrangement; griseocholin; *Streptomyces griseus*.

In 1984, two independent reports described the isolation of new monocarboxylic acid ionophores, griseocholin and antibiotic M 144255 from cultures of *Streptomyces griseus*. These two compounds turned out to be the same monocarboxylic acid ionophore zincophorin [1,2]. Zincophorin exhibited broad in vitro antibiotic activities against gram-positive bacteria as well as *Clostridrium Welchii* [1,2]. Only one total synthesis of this molecule was reported by Danishefsky et al. [3] when we undertook this project.

Retrosynthetic analysis revealed that zincophorin might be constructed using an aldol condensation between compound **A** (fragment C1–C12) and compound **B** (fragment C13–C25), followed by a stereoselective reduction to control the configuration of the C11 stereocenter. The stereochemical outcome of the aldol coupling should be exclusively controlled by the C10 stereocenter present in ethyl ketone **A** [4], as the stereogenic centers in aldehyde **B** are too remote from the carbonyl group to exert any influence on the stereoselectivity. Therefore, the stereochemical relationship between the two methyl groups at C10 and C12 should be *syn* [4] (Fig. 1).

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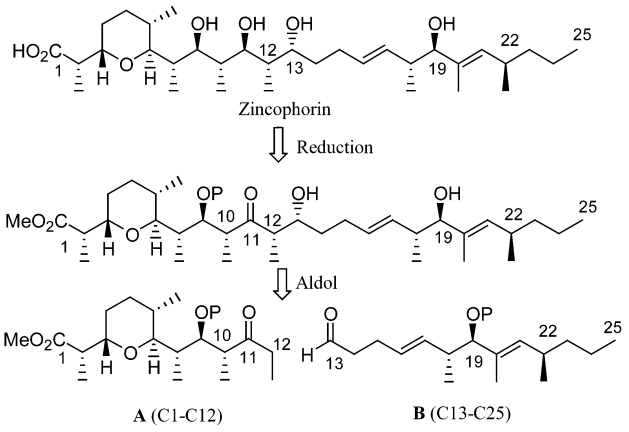

Fig. 1 Retrosynthetic analysis of zincophorin.

The key step in the synthesis of the C1–C12 fragment **A** would rely on the construction of the tetrahydropyran ring by using an intramolecular oxymercuration reaction of a substituted cyclopropanemethanol derivative of type **C**. Nucleophilic attack of the hydroxyl group at C3 should occur stereoselectively with inversion of configuration at C7 [5]. The absolute configurations at C2 and C3 in compound **D** should be controlled by using a chiral auxiliary-mediated aldol condensation between an appropriate chiral enolate and an aldehyde of type **D**. The relative configuration at C6 should be controlled by a diastereoselective hydroboration of an isopropenyl cyclopropane of type **E** [6], and this compound, in turn, should be accessible by nucleophilic ring opening of the optically enriched cyclopropyllactone **2** [7] (Fig. 2).

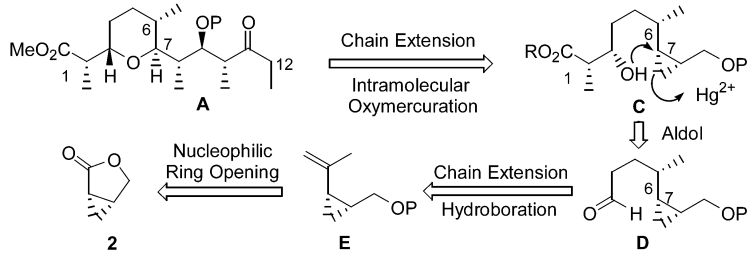

Fig. 2 Retrosynthetic analysis of the C1–C12 fragment of zincophorin.

The intramolecular enantioselective cyclopropanation of allyl diazoacetate **1** catalyzed by the chiral dirhodium complex Rh_2[(5*R*)-MEPY] afforded the cyclopropyllactone (ee = 95 %, 91 %) [8], which was transformed to the isopropenyl cyclopropane **3** (85 %) in two steps (MeLi, subsequent silylation, then MsCl, Et_3N/DMAP) [7]. Compound **3** was then hydroborated in a highly diastereoselective fashion (dr > 96/4) [6] by using BH_3·THF followed by an oxidative alkaline work-up ($NaOH/H_2O_2$), and the resulting alcohol was oxidized to aldehyde **4**. Preparation of the precursor for the elaboration of the oxygen heterocycle by an oxymercuration required the carbon chain extension, and the aldehyde **4** was transformed to **5** in three steps (74 %) involving a Horner–Wadsworth–Emmons reaction followed by hydrogenation of the double bond and reduction of the ester moiety. The next step dealt with the introduction of the C2 and C3 stereocenters with the required absolute configuration, which was accomplished by an aldol reaction involving an (*E*)-boron enolate generated from the chiral ketone **13** [9] and afforded the corresponding aldol **6** with high diastereoselectivity (dr > 96/4, 83 %). After deprotection of **6** with HF·Pyr, the resulting cyclopropanemethanol was subjected to the intramolecular oxymercu-

ration reaction by using $Hg(OCOCF_3)_2$. After reductive demercuration [10] and protection of the primary alcohol, tetrahydropyran **7** was obtained as the major diastereomer (dr = 93/7, 66 %). The next task was to remove the chiral auxiliary used in the aldol condensation without epimerization at C2. Reduction of the carbonyl at C1 and the benzoate was accomplished by using $LiBH_4$, and the resulting diol underwent oxidative cleavage with $NaIO_4$ [9]. Oxidation of the intermediate aldehyde afforded the corresponding carboxylic acid, which was converted to ester **8** (65 %) by treatment with trimethylsilyldiazomethane. After deprotection of the primary alcohol and oxidation, aldehyde **9** was obtained in 90 % yield. A chain extension of this compound as well as the control of the configuration of the C9 and C10 stereogenic centers was achieved by addition of the in situ generated allenylzinc reagent **14** [11]. Compound **10**, possessing the required C8–C9–C10 *anti,anti*-relative configuration, was isolated in 63 % yield (from a separable mixture of three diastereomeric homopropargyl alcohols, dr = 80/12/8) and was then transformed to aldehyde **11** by hydrogenation of the acetylenic functionality, protection of the secondary alcohol, and oxidative cleavage of the double bond. After treatment of aldehyde **11** with an excess of lithium diethylcuprate [12], oxidation of the resulting secondary alcohol afforded ethyl ketone **12** (70 %), which constitutes the C1–C12 subunit of zincophorin (Fig. 3).

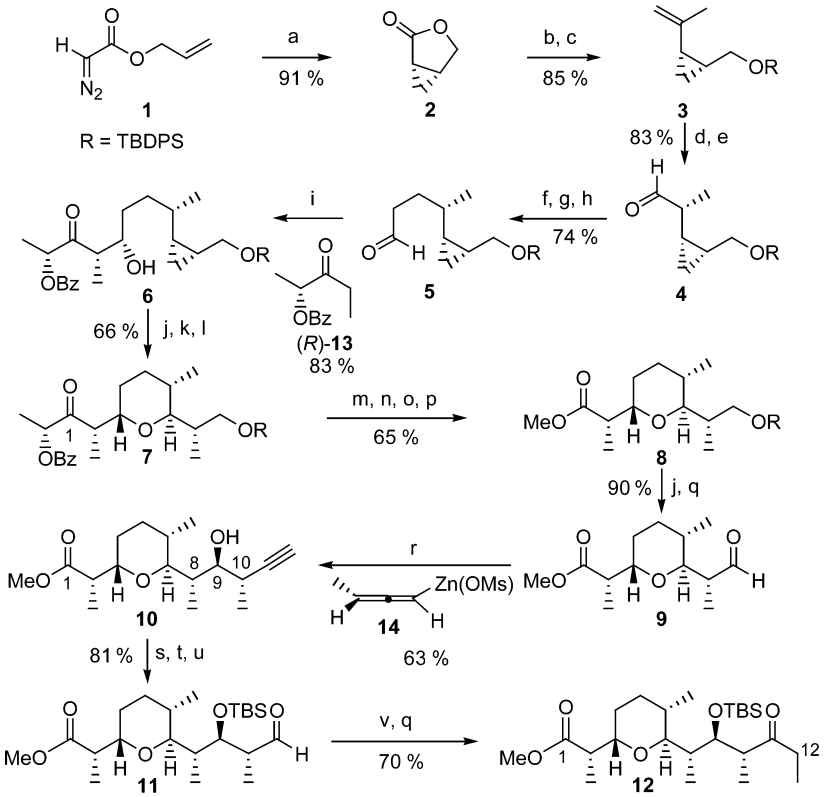

Fig. 3 Synthesis of the C1–C12 fragment of zincophorin. Reagents and conditions: (a) $Rh_2[(5R)\text{-MEPY}]_4$, CH_2Cl_2, reflux, addition of **1** over 30 h; (b) MeLi (2 equiv), THF, 0 °C then TBSCl, imidazole, DMF; (c) $MeSO_2Cl$, Et_3N, DMAP, CH_2Cl_2; (d) BH_3·THF, THF, –30 °C to rt then NaOH, H_2O_2; (e) PCC, MS 4 Å, CH_2Cl_2; (f) $(EtO)_2POCH_2CO_2Et$, NaH, THF; (g) H_2, PtO_2, EtOAc; (h) DIBAL-H, toluene, –78 °C; (i) (*R*)-**13**, *c*-Hex_2BCl, $EtNMe_2$, Et_2O, 0 °C; addition of **5**, –78 °C to –23 °C; (j) HF·Pyr, THF; (k) $Hg(OCOCF_3)_2$, CH_2Cl_2 then KBr/H_2O, then *n*-Bu_3SnH, AIBN, THF/toluene, rt to 60 °C; (l) TBDPSCl, imidazole, DMF, rt; (m) $LiBH_4$, THF; (n) $NaIO_4$, MeOH/H_2O; (o) $NaClO_2$, NaH_2PO_4, 2-methylbut-2-ene, *t*-BuOH/H_2O; (p) Me_3SiCHN_2, MeOH/C_6H_6; (q) Dess–Martin periodinane (DMP), Pyr, CH_2Cl_2; (r) **14**, THF, –30 °C; (s) H_2, Pd/$BaSO_4$, quinoline, toluene; (t) TBSOTf, 2,6-lutidine, CH_2Cl_2, –78 °C; (u) OsO_4, NMO, acetone/H_2O then $NaIO_4$, THF/H_2O; (v) Et_2CuLi, Et_2O, –78 °C.

The preparation of the C13–C25 subunit was next examined. In the retrosynthetic analysis of aldehyde **B**, the formation of the C16–C17 disubstituted (*E*)-alkene was envisaged by performing the *anti*-reduction of the triple bond in the disubstituted alkyne **F**. A [3,3]-sigmatropic rearrangement applied to **G** should create the C20–C21 trisubstituted (*E*)-alkene and control the configuration at C22 by a chirality transfer [13]. The choice of the configuration of the tertiary alcohol at C20 and the configuration of the propenyl unit were therefore crucial issues to consider. Because of its excellent coordinating ability, the methoxymethyl (MOM) protecting group was chosen for the hydroxyl at C19 so that the propenyl moiety could be introduced by nucleophilic addition to the carbonyl group of methyl ketone **H** according to the Cram-chelated model [14]. The methyl ketone **H** could be synthesized by addition of a chiral allenylzinc reagent [15] to aldehyde **I** derived from L-ethyl lactate (Fig. 4).

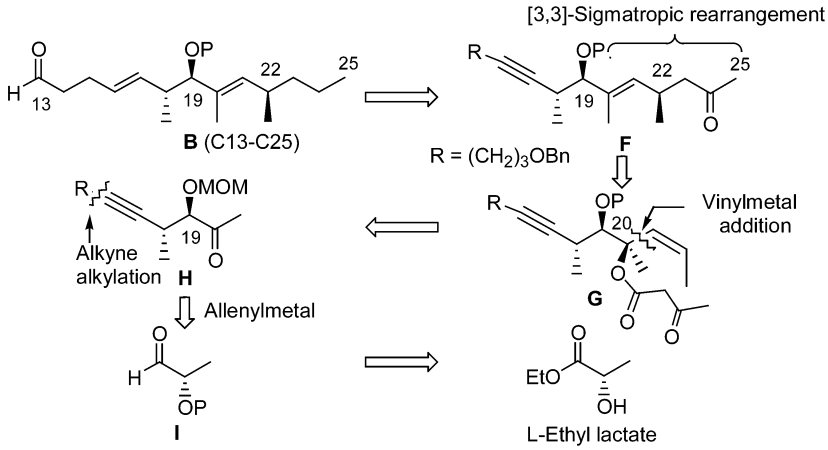

Fig. 4 Retrosynthetic analysis of the C13–C25 fragment of zincophorin.

Aldehyde **15** was prepared in two steps from L-ethyl lactate and treated with the chiral allenylzinc **24** to afford the homopropargylic alcohol **16** (dr > 96/4, 75 %) [15]. Ketone **17**, which was obtained in three steps from **16** (alkyne alkylation, deprotection, and oxidation), was treated with (*Z*)-prop-1-enylmagnesium bromide in the presence of an excess of $MgBr_2 \cdot OEt_2$. Diol **18** was obtained (93 %, dr = 9/1) in agreement with the Cram-chelated model [14]. After reaction of **18** with diketene, the tertiary acetoacetate **19** was obtained (88 %), and a stereoselective Carroll–Claisen rearrangement was successfully performed on neutral alumina [16] to produce methyl ketone **20** (72 %). However, in compound **20**, the secondary alcohol moiety at C19 was protected as a MOM ether, and its deprotection at a later stage in the synthesis turned out to be difficult. Thus, the MOM group was replaced by a TBS group. At first, ketone **20** was transformed to **21** in four steps (carbonyl reduction, mesylation, reduction, and MOM deprotection, 70 %). Due to the presence of the free hydroxyl group at the homopropargylic position, the reduction of the triple bond in compound **21** could be achieved by using $LiAlH_4$ to afford the (*E*)-homoallylic alcohol **22** (61 %). Aldehyde **23** was obtained from **22** after silylation, cleavage of the benzyl ether followed by oxidation of the resulting primary alcohol (Fig. 5).

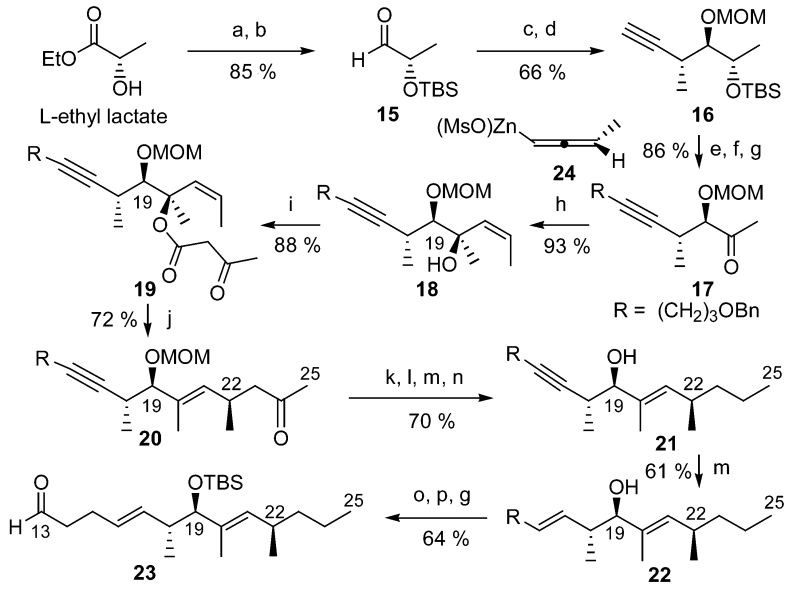

Fig. 5 Synthesis of the C13–C25 fragment of zincophorin. Reagents and conditions: (a) TBSCl, imidazole, THF; (b) DIBAL-H, Et_2O, –40 °C; (c) **24**, THF, –20 °C; (d) MOMCl, *i*-Pr_2NEt, CH_2Cl_2; (e) *n*-BuLi, THF, –78 °C then $BnO(CH_2)_3Br$, HMPA, –78 °C to rt; (f) *n*-Bu_4NF, THF; (g) DMP, Pyr, CH_2Cl_2; (h) (*Z*)-(Prop-1-enyl)MgBr, $MgBr_2{\cdot}OEt_2$, THF/Et_2O, –78 °C; (i) Diketene, cat. DMAP, THF, rt; (j) Adsorption on Al_2O_3, 60 °C; (k) DIBAL-H, Et_2O, –78 °C; (l) MsCl, *i*-Pr_2NEt, CH_2Cl_2, 0 °C; (m) $LiAlH_4$, THF, reflux; (n) *p*-TsOH, MeOH, rt; (o) TBSOTf, 2,6-lutidine, CH_2Cl_2, –78 °C; (p) Li, liq. NH_3, THF/*t*-BuOH.

Having synthesized ethyl ketone **12** (C1–C12 subunit) and aldehyde **23** (C13–C25 subunit), their coupling by using an aldol reaction was achieved. Due to the C12–C13 *syn*-relative configuration, it was necessary to achieve the addition of the (*Z*)-titanium enolate **25** [4] derived from ethyl ketone **12** to aldehyde **23**. This aldol reaction afforded compound **26** with high diastereoselectivity (dr = 96/4) having a *syn* relationship between the methyl groups at C10 and C12. The completion of the total synthesis of zincophorin methyl ester **27** was achieved by a diastereoselective reduction of the carbonyl group at C11 with $NaBH_4$ in methanol, and the corresponding diol was directly treated with HF·Pyr in THF to deprotect the alcohol functionalities at C9 and C19. Zincophorin methyl ester **27** was obtained from aldol **26** in 66 % yield and then transformed to zincophorin with aqueous LiOH in THF/methanol at 50 °C (Fig. 6).

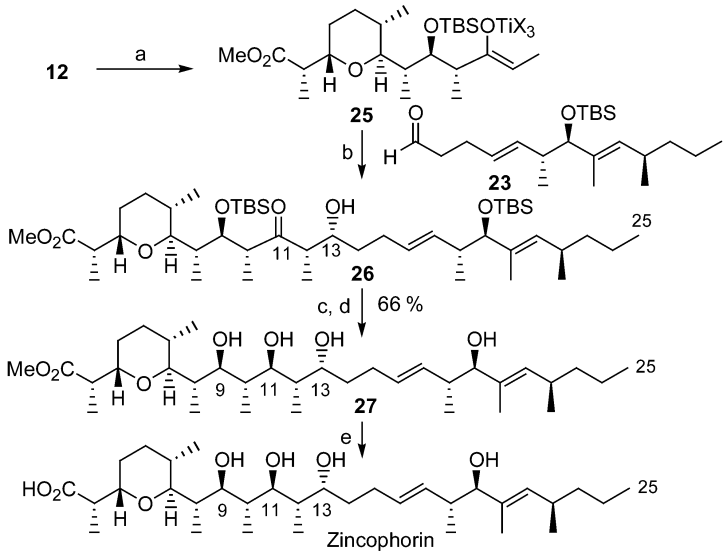

Fig. 6 Synthesis of the methyl ester of zincophorin and zincophorin. Reagents and conditions: (a) $TiCl_4$, *i*-Pr_2NEt, CH_2Cl_2, –78 °C; (b) Addition of aldehyde **23**, –78 °C, 2 h; (c) $NaBH_4$, MeOH, 0 °C; (d) HF·Pyr, THF; (e) LiOH, H_2O/MeOH/THF, 50 °C.

In conclusion, we have completed the second synthesis of zincophorin by a convergent strategy involving the coupling of the C1–C12 and C13–C25 subunits using a highly diastereoselective titanium-mediated aldol condensation [17]. The synthesis of the C1–C12 fragment, which was accomplished in 25 steps from allyl diazoacetate (6 % overall yield), illustrated the synthetic potential of an intramolecular oxymercuration of a cyclopropanemethanol derivative for the elaboration of the trisubstituted tetrahydropyran. The preparation of the C13–C25 subunit was achieved in 18 steps from L-ethyl lactate (7 % overall yield), and relied on a stereoselective Caroll–Claisen rearrangement of a tertiary allylic acetoacetate.

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