ORGANIC LETTERS

2003
Vol. 5, No. 22
4037−4040

Total Synthesis of Zincophorin Methyl Ester

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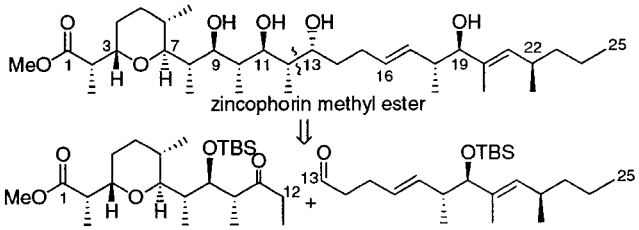
Received June 25, 2003

ABSTRACT

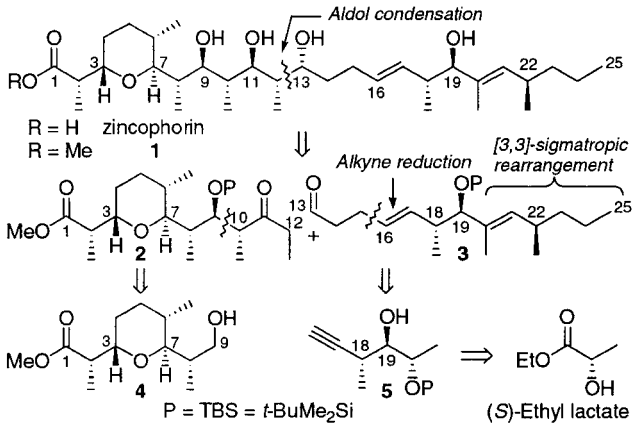


A convergent total synthesis of the methyl ester of zincophorin, an ionophore antibiotic, has been realized relying on a diastereoselective titanium-mediated aldol coupling between the C1–C12 and C13–C25 subunits. The latter fragment was prepared by using a Carroll–Claisen rearrangement.

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.[1,2] 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).[3,4] Zincophorin exhibits good in vitro activity against Gram-positive bacteria,[3,4] and its methyl ester also possesses antiviral activity, with reduced host cell toxicity compared to the free acid.[5] Although the preparation of elaborated fragments of zincophorin has been reported,[6−8] to date, only a single total synthesis has been completed by Danishefsky's group.[6] Herein, we report a total synthesis of zincophorin methyl ester **1** featuring new approaches toward the preparation and the coupling of two subunits.

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

Scheme 1. Structure of Zincophorin and Retrosynthetic Disconnections



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10.1021/ol035177n CCC: $25.00
Published on Web 10/08/2003

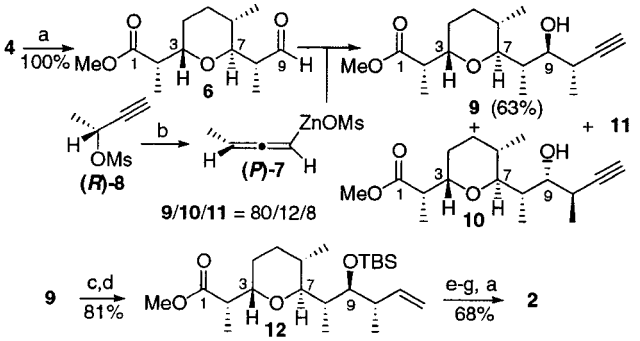
been recognized to be the most difficult to synthesize,[9] a plausible disconnection was the C12−C13 bond, and in the forward sense, its construction was envisaged by performing an aldol condensation between the (*Z*)-enolate derived from ethyl ketone **2** and aldehyde **3**. The ethyl ketone **2** could be prepared by an appropriate stereoselective chain extension of alcohol **4** incorporating the C1−C9 subunit of zincophorin.[8] 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.[10] 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.[8] 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.[9]

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.[7h,9,11] 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.[12] 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.[13−15] The synthesis of the C1−C12 subunit of zincophorin was then pursued from

Scheme 2. Synthesis of the C1−C12 Subunit of Zincophorin[a]



[a] Reagents and conditions: (a) DMP, pyr, CH_2Cl_2; (b) (*R*)-**8**, cat. $Pd(OAc)_2$, PPh_3, Et_2Zn, THF, −30 °C; (c) H_2, cat. $Pd/BaSO_4$, quinoleine, toluene; (d) TBSOTf, 2,6-lutidine, CH_2Cl_2, −78 °C; (e) cat. OsO_4, NMO, acetone−H_2O; (f) $NaIO_4$, THF−H_2O; (g) Et_2CuLi, Et_2O, −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).[10] 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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(9) (a) Hoffmann, R. W. *Angew. Chem., Int. Ed. Engl.* **1987**, *26*, 489. (b) Hoffmann, R. W. *Synthesis* **1994**, 629.

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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**.

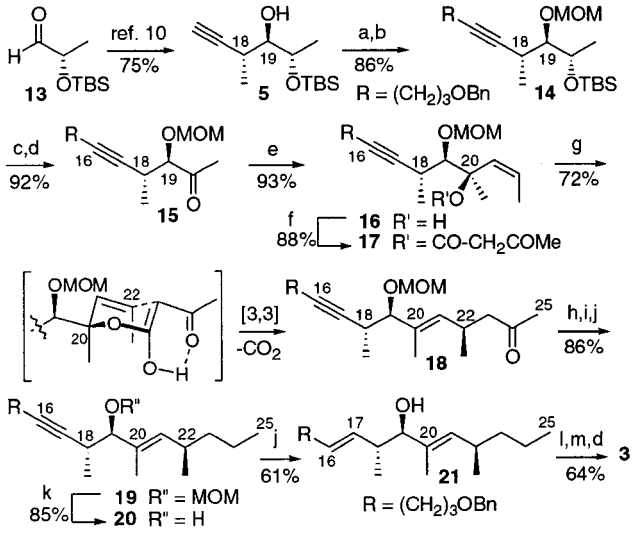
(14) Condensation of aldehyde **6** with the chiral (*E*)-crotylcyclopentadienyl-[(4*R*,5*R*)-2,2-dimethyl-1,3-dioxolane-4,5-diphenylmethanolato]titanium reagent[15] also occurred in the mismatched manifold and afforded a 70/30 diastereomeric mixture of two homoallylic alcohols of *anti* relative configuration 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.[12] 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**.

(15) Hafner, A.; Duthaler, R. O.; Marti, R.; Rihs, G.; Rothe-Streit, P.; Schwarzenbach, F. *J. Am. Chem. Soc.* **1992**, *114*, 2321. (b) BouzBouz, S.; Cossy, J. *Org. Lett.* **2001**, *3*, 3995.

(92%). The Cram-chelated addition[11] 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,[16] reaction with diketene in the presence of a catalytic amount of DMAP proceeded smoothly to afford the β-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[16,17] 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 β-ketoester **17** on neutral alumina, followed by heating at 60 °C,[18] 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).[19,20]

Scheme 3. Synthesis of the C13−C25 Subunit of Zincophorin[a]

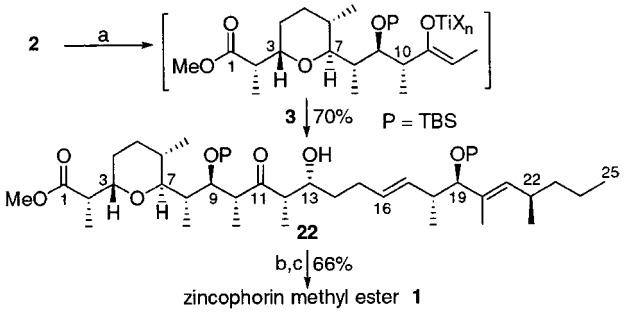


[a] Reagents and conditions: (a) MOMCl, *i*-Pr_2NEt, CH_2Cl_2; (b) *n*-BuLi, THF, −78 °C then RBr, HMPA, −78 °C to room temperature; (c) TBAF, THF; (d) DMP, pyr, CH_2Cl_2; (e) (*Z*)-prop-1-enylMgBr, $MgBr_2{\cdot}OEt_2$, Et_2O−THF, −78 °C; (f) diketene, cat. DMAP, THF; (g) neutral Al_2O_3, 60 °C; (h) DIBAL-H, Et_2O, −78 °C; (i) MsCl, *i*-Pr_2NEt, CH_2Cl_2, 0 °C; (j) $LiAlH_4$, THF, reflux; (k) *p*-TsOH, MeOH; (l) TBSOTf, 2,6-lutidine, CH_2Cl_2, −78 °C; (m) Li, liq. NH_3, THF−*t*-BuOH, −78 °C. R = $(CH_2)_3OBn$.

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 $LiAlH_4$ 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 $LiAlH_4$ 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[a]



[a] Reagents and conditions: (a) $TiCl_4$, *i*-Pr_2NEt, CH_2Cl_2, −78 °C, then add **3**, −78 °C; (b) $NaBH_4$, MeOH, 0 °C; (c) HF·pyr, THF.

On the basis of literature precedents, the stereochemical outcome of the aldol condensation between the (*Z*)-titanium enolate[21] of **2** and aldehyde **3** lacking α and β stereocenters was anticipated to be exclusively controlled by the configuration of the methyl-substituted C10 stereocenter.[22] Accordingly, the (*Z*)-titanium enolate of ethyl ketone **2** was

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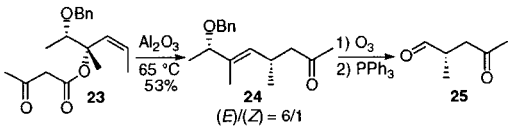
(19) This result could be explained on the basis of the well-established preference for the [3,3]-sigmatropic rearrangements to proceed through a chairlike transition state (acyclic series),[16] in which the bulkier branched carbon chain, rather than the methyl group, should preferentially occupy the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

(20) Carroll rearrangement of the related tertiary allylic β-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).



(21) Evans, D. A.; Rieger, D. L.; Bilodeau, M. T.; Urpi, F. *J. Am. Chem. Soc.* **1991**, *113*, 1047.

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generated in the standard manner[21,22] 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 $NaBH_4$ 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_f in two solvent systems,[5] IR,[5,6] ^{1}H NMR spectra,[6] and $[\alpha]_D$ +21.3 (*c* 0.4, $CHCl_3$) were in perfect agreement with those previously reported in the literature ($[\alpha]_D$ +22.4 (*c* 0.89, $CHCl_3$);[6] authentic sample, $[\alpha]_D$ +20.9 (*c* 2.0, $CHCl_3$)[1,6]). 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_2N_2 to afford **1**.[6]

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 β-ketoester, and a chain extension of the previously synthesized C1−C9 fragment[8] 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.[23]

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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