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Total Synthesis of Zincophorin and Its Methyl Ester

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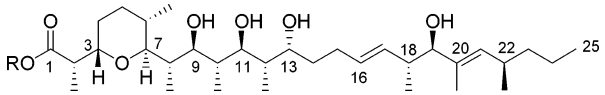
A total synthesis of the naturally occurring ionophore zincophorin has been realized. The route features an intramolecular oxymercuration of a cyclopropanemethanol and a Carroll−Claisen rearrangement for the respective elaboration of the C1−C12 and C13−C25 subunits, which have been assembled by using a highly diastereoselective titanium-mediated aldol condensation.

Introduction

The useful antiinfectious properties displayed by many naturally occurring polyoxygenated ionophores have been explained by their capacities to form lipophilic complexes with various cations, usually alkaline or alkaline-earth ones, which affect proton−cation exchange processes across biological membranes.[1,2] In 1984, two independent reports described the isolation of new monocarboxylic acid ionophores, griseocholin[3] and antibiotic M144255,[4] from cultures of strains of *Streptomyces griseus*. The structure of griseocholin was first established by extensive NMR experiments,[3,5] whereas the three-dimensional structure of antibiotic M144255, including its absolute configuration, was ascertained by X-ray diffraction of its zinc−magnesium salt.[4] In fact, these two compounds turned out to be the same monocarboxylic acid ionophore **1** (Figure 1).[4] Of considerable interest from the pharmacological perspective was the remarkable affinity exhibited by this ionophore for divalent cations and especially zinc, on the basis of which it was given the trivial name zincophorin. Zincophorin and its calcium salt exhibited broad in vitro antibiotic activities against Gram-positive bacteria as well as *Clostridium welchii*.[3,4] The ammonium and sodium salts of zincophorin showed significant anticoccidal activity against *Eimeria tenella* in chicken embryos.[3,4] Moreover, the methyl ester of zincophorin **2** was reported to possess antiviral activity with reduced host cell toxicity compared to the free acid.[6,7] Zincophorin has elicited considerable synthetic interest as the preparation of elaborated fragments has been reported.[8−15] However, only one single total synthesis was accomplished by Danishefsky et al. in 1988, which highlighted the potential of Lewis acid promoted cyclocondensation between silyloxydienes and aldehydes as a route toward oxygen heterocycles as well as polypropionate units.[8]



1 R = H Zincophorin
2 R = Me Zincophorin methyl ester

FIGURE 1. Structure of zincophorin and its methyl ester.

Herein, we report a full account of our studies concerning the total synthesis of zincophorin and its methyl ester, featuring new approaches toward the preparation and the coupling of two subunits.

The twenty-five carbon backbone of zincophorin contains a number of interesting structural elements usually encountered in polypropionates, such as a propionic acid unit branched at C2 with a trisubstituted tetrahydropyran (C3−C7), alternate methyl and hydroxyl groups (C8−C13 and C18−C19), one disubstituted double bond (C16−C17) and a trisubstituted one (C20−C21) both of (*E*) configuration, and a remote isolated stereocenter (C22). We set ourselves the challenging goal of disconnecting the carbon framework within the characteristic C9−C13 polypropionate-type segment and obtain zincophorin and its methyl ester from an aldol of type **A**, by achieving

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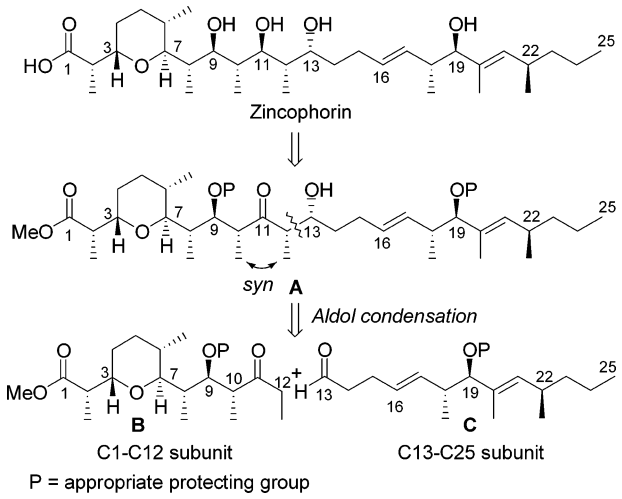
SCHEME 1. Retrosynthetic Analysis of Zincophorin



the diastereoselective reduction of the carbonyl group at C11 and subsequent deprotection steps. As *anti*,*anti*-methyl-hydroxyl-methyl arrays have been recognized to be difficult to synthesize,[13,16] a plausible disconnection in the aldol **A** appeared to be the C12−C13 bond. Due to the *syn* relationship between the methyl group at C12 and the hydroxyl group at C13, the construction of the C12−C13 bond was envisaged by using an aldol condensation between the (*Z*)-enolate derived from an ethyl ketone of type **B** (C1−C12 subunit) and an aldehyde of type **C** (C13−C25 subunit). The stereochemical outcome of the aldol coupling should be exclusively controlled by the C10 stereocenter present in ethyl ketone **B** as the stereogenic centers in the aldehyde **C** 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 in the aldol **A** should be *syn* (Scheme 1).[17]

Having identified the key disconnection in the retrosynthetic analysis of zincophorin, the preparation of the corresponding C1−C12 and C13−C25 subunits was examined.

Results and Discussion

In the retrosynthetic analysis of the C1−C12 subunit of type **B**, it was envisaged to install the C9 and C10 stereocenters with the required absolute configurations by achieving a stereoselective carbon chain extension of the aldehyde of type **D** (C1−C9 subunit). The original key stage of our synthetic plan relied on the construction of the tetrahydropyran ring by using an intramolecular oxymercuration reaction of an appropriately substituted cyclopropanemethanol derivative of type **E**.[18] Whereas the intramolecular oxymercuration of alkenes or related compounds has been widely used to synthesize oxygen heterocycles and especially those encountered in the structures of naturally occurring ionophores,[19,20] the corresponding reaction with cyclopropane derivatives has received much less attention in the context of natural product synthesis. On the basis of literature precedents and our investigations,[18,21,22] it was anticipated that the electrophilic ring-opening reaction of the three-membered ring in compound **E** with mercury(II) salts should occur regioselectively at the most electron-rich bond, due to the negative inductive effect of the hydroxyalkyl substituent. Moreover, concomitant nucleophilic attack of the hydroxyl group (at C3) should occur stereoselectively and should lead to an inversion of configuration at C7.[18,21,22] Subsequent reductive demercuration[23] would enable the installation of the methyl group at C8. The absolute configurations at C2 and C3 in the requisite oxymercuration precursor of type **E** could be controlled by using a chiral auxiliary-mediated aldol condensation between an appropriate chiral enolate and an aldehyde of type **F**, which incorporates three contiguous stereocenters (C6−C8). On the basis of our previous studies,[24] the relative configuration at C6 could be controlled by achieving a diastereoselective hydroboration of an isopropenylcyclopropane of type **H** followed by a chain extension sequence in order to transform the resulting alcohol **G** to the aldehyde of type **F**. Finally, the isopropenylcyclopropane of type **H** could be prepared by nucleophilic ring-opening of the optically enriched cyclopropyl lactone **3** (Scheme 2).[25,26] To study the influence of the protecting group in the intramolecular oxymercuration of the cyclopropanemethanol derivative of type **E**, the use of a *tert*-butyldiphenylsilyl ether (P = TBDPS) and a benzyl group (P = Bn) were considered for the alcohol moiety at C9.

The intramolecular enantioselective cyclopropanation of allyl diazoacetate catalyzed by Doyle's chiral dirhodium

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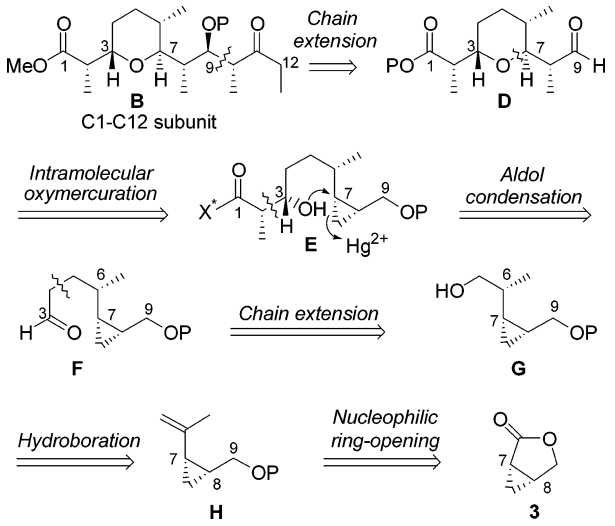
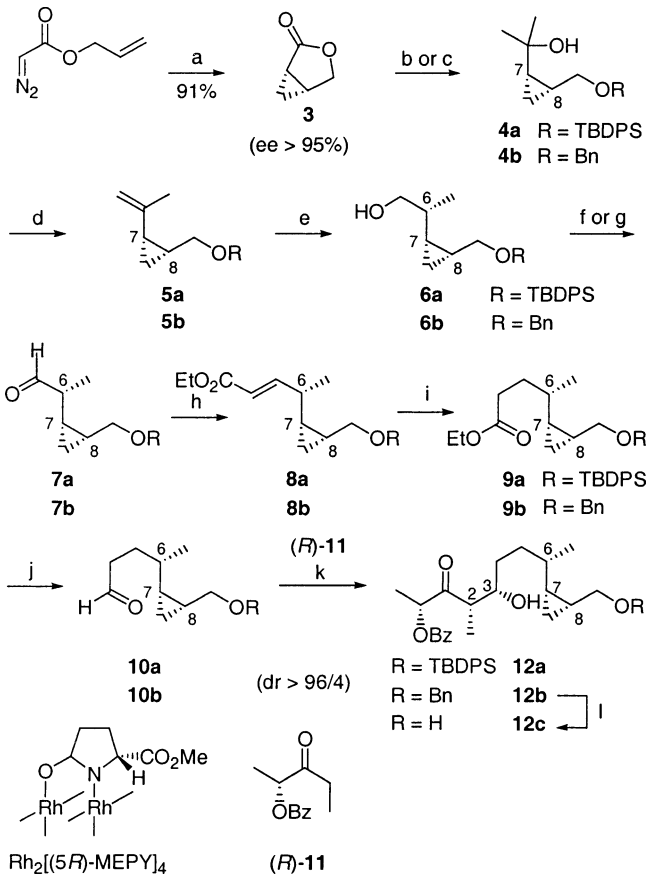
SCHEME 2. Retrosynthetic Analysis of the C1−C12 Subunit



complex $Rh_2((5R)\text{-MEPY})_4$ (0.1 mol %) afforded (1*S*,5*R*)-3-oxabicyclo[3.1.0]hexan-2-one **3** (ee ≥ 95%, 91%).[26,27] The cyclopropyl lactone **3** was treated with two equivalents of methyllithium and the subsequent silylation of the primary lithium alkoxide was carried out by addition of a mixture of *tert*-butyldiphenylsilyl chloride and imidazole to afford the silyl ether **4a** in excellent yield (90%). By contrast, the in situ benzylation of the primary lithium alkoxide with benzyl bromide was extremely sluggish even in the presence of polar cosolvents (HMPA or DMSO). Therefore, after ring-opening of the cyclopropyl lactone **3** with methyllithium, the reaction mixture was quenched with 50% aqueous NaOH, and subsequent benzylation under phase-transfer catalysis afforded the benzyl ether **4b** (89%). The tertiary alcohols **4a** and **4b** were then dehydrated by using a large excess of methanesulfonyl chloride and triethylamine in the presence of a stoichiometric amount of DMAP in dichloromethane at 0 °C, and the isopropenylcyclopropanes **5a** (85%) and **5b** (83%) were obtained (Scheme 3).[25] To introduce the new stereocenter at C6, adjacent to the three-membered ring, the protected alcohols **5a** and **5b** were hydroborated with BH_3·THF complex in THF. After a standard oxidative alkaline workup with H_2O_2/NaOH, the corresponding primary alcohols **6a** (91%) and **6b** (91%) were obtained in a highly diastereoselective fashion (dr > 96/4). The relative configuration of the newly introduced stereocenter in compounds **6a** and **6b** was assigned according to our previous investigations concerning the diastereoselectivity of electrophilic additions to alkenyl-substituted three-membered rings.[24]

The preparation of suitable precursors for the elaboration of the oxygen heterocycle by an intramolecular oxymercuration required the carbon chain extension,[28] as well as the introduction of the C2 and C3 stereocenters. The oxidation of the primary alcohol **6a** could be efficiently carried out with PCC to afford aldehyde

SCHEME 3 [a]



[a] Reagents and conditions: (a) $Rh_2((5R)\text{-MEPY})_4$ (0.1 mol %), CH_2Cl_2, reflux, addition of allyl diazoacetate over 30 h (91%); (b) MeLi (2 equiv), THF, 0 °C then TBDPSCl, imidazole, DMF, rt (90%); (c) MeLi (2 equiv), THF, 0 °C then 50% aq NaOH, toluene, BnBr, cat. $BnNEt_3Cl$ (89%); (d) $MeSO_2Cl$, Et_3N, DMAP, CH_2Cl_2, 0 °C (**5a**: 85%, **5b**: 83%); (e) BH_3·THF, THF, −30 °C to rt then NaOH, H_2O_2 (**6a** and **6b**: 91%); (f) PCC, 4 Å molecular sieves, CH_2Cl_2 (91%); (g) cat. TPAP, NMO, CH_2Cl_2/MeCN (9/1), 0 °C; (h) $(EtO)_2P(O)CH_2COOEt$, NaH, THF, (**8a**: 78% from **6a**, **8b**: 56% from **6b**); (i) H_2, cat. PtO_2, EtOAc (**9a**: 98%, **9b**: 95%); (j) Dibal-H, toluene, −78 °C (**10a**: 97%, **10b**: 90%); (k) (*R*)-**11**, *c*-Hex_2BCl, $EtNMe_2$, Et_2O, 0 °C then addition of aldehyde **10a** or **10b**, −78 to −23 °C (**12a**: 83%, **12b**: 87%); (l) HF·Pyr, THF (86%).

7a,[29] whereas the oxidation of the primary alcohol **6b** was carried out with the mild reagent TPAP/NMO[30] and the unstable aldehyde **7b** was directly engaged in the next step. A Horner−Wadsworth−Emmons reaction was used in order to perform the carbon chain extension of aldehydes **7a** and **7b** and provided the corresponding (*E*)-α,β-unsaturated esters **8a** (78% from **6a**) and **8b** (56% from **6b**). The double bond in these compounds was hydrogenated over PtO_2 in ethyl acetate to give esters **9a** (98%)

(27) The ring-opening of the enantiomerically enriched cyclopropyl lactone **3** and racemic (±)-**3** with (*S*)-phenylethylamine (ee > 99%), in the presence of 2-hydroxypyridine, afforded a mixture of diastereomeric amides. Quantification of these diastereomers in both cases by ^1H NMR confirmed an ee value greater than 95% for **3**; see: Schotten, T.; Boland, W.; Jaenicke, L. *Tetrahedron Lett.* **1986**, *27*, 2349.

(28) The hydroboration of **5a** and **5b** was also carried out with 9-BBN-H, but the homologation of the resulting organoborane 9-BBN-B-alkyl did not proceed readily in the presence of carbenoid type reagents such as the potassium enolate of methylbromoacetate or chloroacetonitrile, according to: (a) Brown, H. C.; Nambu, H.; Rogic, M. *J. Am. Chem. Soc.* **1969**, *91*, 6852. (b) Brown, H. C.; Nambu, H.; Rogic, M. *J. Am. Chem. Soc.* **1969**, *91*, 6854.

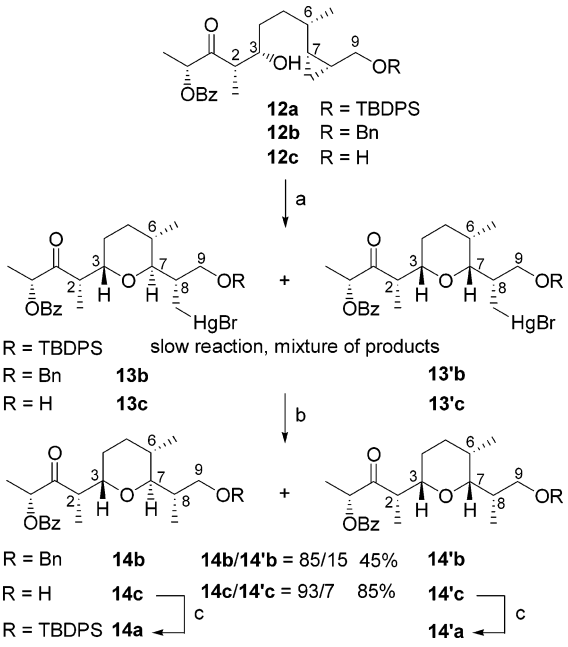
(29) Several oxidizing reagents could be used, and none of them caused epimerization at C6. On a large scale, PCC turned out to be the most convenient: Corey, E. J.; Suggs, J. W. *Tetrahedron Lett.* **1975**, 2647.

(30) Ley, S. V.; Norman, J.; Griffith, W. P.; Marsden, S. P. *Synthesis* **1994**, 639.

and **9b** (95%), respectively. Finally, the reduction of these two ethyl esters with Dibal-H in toluene at −78 °C afforded aldehydes **10a** (97%) and **10b** (90%). The next step dealt with the introduction of the C2 and C3 stereocenters with the required absolute configurations. An auxiliary-mediated enantioselective aldol condensation appeared an attractive option for this purpose since in aldehydes **10a** and **10b** the stereogenic centers were too remote from the carbonyl group to act as efficient stereochemical control elements. The *anti* relative configuration of the C2 and C3 stereocenters entailed the involvment of an (*E*)-enolate and the methodology developed by Paterson, based on the use of the boron enolates generated from chiral ethyl ketones derived from lactic acids, was selected.[31] The required ethyl ketone (*R*)-**11**, prepared in three steps from the commercially available (*R*)-isobutyl lactate, was converted to an (*E*)-boron enolate by treatment with chlorodicyclohexylborane in the presence of *N*,*N*-dimethylethylamine as a base, and condensation with aldehydes **10a** and **10b** afforded the corresponding aldol products **12a** (83%) and **12b** (87%), respectively, with high diastereoselectivity (dr > 96/4).[31] The hydroxyl group at C9 in compound **12a** was deprotected by treatment with HF·Pyridine complex in THF to afford the cyclopropanemethanol **12c** (86%) (Scheme 3).

The feasibility of the next crucial transformation, involving the elaboration of the oxygen heterocycle by an intramolecular oxymercuration of the three-membered ring, could then be tested with the three substrates **12a**−**c**. Thus, when the silyl ether **12a** was treated with mercuric trifluoroacetate in dichloromethane,[18,21,22] a slow and incomplete reaction occurred and a complex mixture of products was generated. As the *tert*-butyldiphenylsilyl protecting group may interfere with the oxymercuration,[22] the same sequence was applied to the benzyl ether **12b**. In this case, the oxymercuration occurred rapidly, and after treatment of the reaction mixture with a saturated aqueous solution of KBr, the analysis of the ^{1}H NMR spectrum of the crude material indicated the plausible formation of two diastereomeric organomercuric bromides **13b** and **13′b** (85/15 ratio). With the aim of minimizing the handling of organomercurials, a reductive demercuration was directly carried out by using *n*-Bu_3SnH and a catalytic amount of AIBN[32] in THF/toluene (1/1, rt to 60 °C) followed by destruction of the excess tin hydride with CCl_4[20] and subsequent washings with an aqueous solution of KF. Unlike the oxymercuration which had proceeded in virtually quantitative yield, several byproducts were generated during the reductive demercuration, and an 85/15 diastereomeric mixture of tetrahydropyrans **14b** and **14′b** was isolated in only 45% yield. Much better results were obtained in the case of the unprotected cyclopropanemethanol **12c**. Indeed, when this compound was subjected to the oxymercuration reaction, a diastereomeric mixture of heterocyclic organomercuric bromides **13c** and **13′c** was formed and fortunately in this case, the reductive demercuration proceeded extremely cleanly to afford a 93/7 diastereomeric mixture of the tetrahydropyrans **14c** and **14′c** in 85% yield. After protection of the primary hydroxyl group at C9 as a *tert*-butyldiphenylsilyl ether, the two diastereomers **14a** and **14′a** were separated by flash chromatography and isolated in 93% and 6% yield respectively (Scheme 4).

SCHEME 4. Elaboration of the Tetrahydropyran Ring by an Intramolecular Oxymercuration[a]



[a] Reagents and conditions: (a) $Hg(OCOCF_3)_2$, CH_2Cl_2, rt then KBr/H_2O; (b) *n*-Bu_3SnH, cat. AIBN, THF/toluene (1/1), rt to 60 °C, then CCl_4 and KF/H_2O; (c) TBDPSCl, imidazole, DMF, rt (**14a**: 93%, **14′a**: 6%).

The relative configurations of the heterocyclic compounds were assigned by ^{1}H NMR studies on the basis of the observed differential nuclear Overhauser effects (NOE), indicating that **14a** and **14′a** were epimeric at C7 and that the major diastereomer **14a** exhibited the required *trans* stereochemical relationship between H3 and H7 for the synthesis of zincophorin.[15a]

This result confirmed that whereas the intramolecular oxymercuration of the cyclopropanes **12b** or **12c** occurred with a very high level of regioselectivity, the nucleophilic attack of the hydroxyl group proceeded predominantly, but not exclusively, with inversion of configuration at C7.[18,21] Thus, the electrophilic ring-opening reaction occurred at the more electron-rich bond of the three-membered ring, which is less subjected to the electron-withdrawing inductive effect of the hydroxymethyl substituent.[18,21−22] This electrophilic ring-opening could be accompanied by the synchronous stereoselective *anti*-nucleophilic attack of the internal hydroxyl group at C3, leading to an inversion of configuration at C7 and affording **13c** (or **13b**) (eq 1) (Scheme 5). Alternatively, a nonsynchronous process, wherein cyclopropane bond breaking and intramolecular nucleophilic attack would not occur at the same rate and would lead to a carbocationic intermediate, could be invoked in order to explain the formation of the epimeric compounds **13′c** (or **13′b**) at C7 (eq 2) (Scheme 5).[33]

Therefore, as it had been envisaged in our synthetic plan, the intramolecular oxymercuration of the nonpro-

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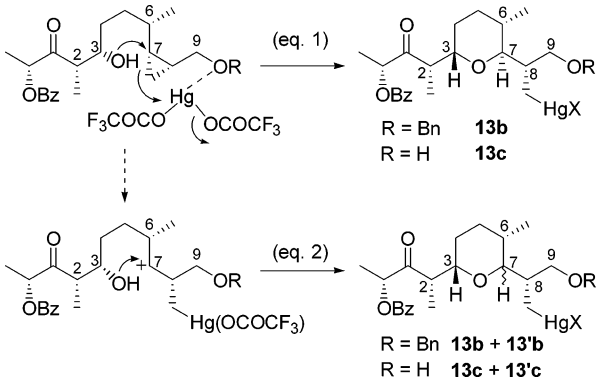
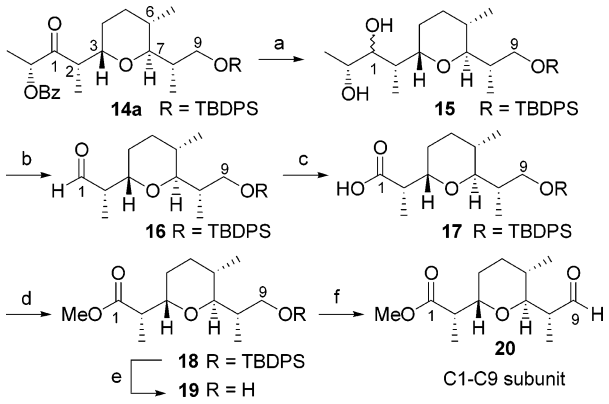
SCHEME 5



tected cyclopropanemethanol **12c** efficiently enabled the construction of the trisubstituted tetrahydropyran of zincophorin in good yield (85%) and with high diastereoselectivity (dr = 93/7) (Scheme 4). Comparatively, the oxymercuration−reductive demercuration of the cyclopropanemethanol protected as a benzyl ether **12b** afforded the oxygen heterocycle **14b** with acceptable diastereoselectivity (dr = 85/15) but with unsatisfactory yield (45%). Furthermore, it appeared that the selection of a *tert*-butyldiphenylsilyl protecting group rather than a benzyl group (for the alcohol moiety at C9) from the beginning of the synthesis of the C1−C9 subunit of zincophorin resulted in higher yields and product stabilities despite an additional deprotection step before and a protection step after the key oxymercuration step.

The synthesis of zincophorin was then pursued from compound **14a** in which the hydroxyl group at C9 had been reprotected as a silyl ether, and the next task was to remove the chiral auxiliary used in the aldol condensation without epimerization of the stereocenter at C2. The reduction of both the carbonyl group at C1 and the benzoate was accomplished by using lithium borohydride in THF.[31] The resulting diol **15** was subjected to an oxidative cleavage with sodium periodate in methanol to afford aldehyde **16**, which was oxidized to the corresponding carboxylic acid **17**.[34] These three reactions, which proceeded cleanly and did not require purification of the intermediate compounds, provided the carboxylic acid **17** with an excellent overall yield of 90% from **14a**. Esterification of **17** with trimethylsilyldiazomethane[35] gave the methyl ester **18** (85%) and subsequent deprotection with HF·Pyridine afforded the primary alcohol **19** (90%). This latter compound was quantitatively oxidized by Dess−Martin periodinane (DMP)[36] to aldehyde **20**, which constitutes the C1−C9 subunit of zincophorin.[15a] Aldehyde **20** turned out to be stable and no epimerization occurred at C8, provided that the remaining traces of pyridine had been properly removed

SCHEME 6. Synthesis of the C1−C9 Subunit of Zincophorin[a]



[a] Reagents and conditions: (a) $LiBH_4$, THF, −20 °C to rt; (b) $NaIO_4$, MeOH/H_2O; (c) $NaClO_2$, NaH_2PO_4, 2-methylbut-2-ene, *t*-BuOH/H_2O, (90% from **14a**); (d) $Me_3SiCH{=}N_2$, MeOH/C_6H_6 (85%); (e) HF·Pyr, THF (90%); (f) DMP, Pyr, CH_2Cl_2 (100%).

from the crude material. Moreover, this compound could be also purified by flash chromatography on silica gel without any epimerization (Scheme 6).

The carbon chain extension of aldehyde **20** could then be investigated with the aim of synthesizing a C1−C12 subunit precursor of type **I** but this operation, which required the installation of two new stereocenters (C9 and C10), was considered to be a challenging task due to the *anti*,*anti* relative configuration of the C8−C10 stereotriad. The use of (*E*)-enolates, (*E*)-crotylmetals or allenylmetals was considered in order to effect the desired transformation. However, the *anti* stereochemical relationship between the methyl group at C8 and the hydroxyl group at C9 suggested that the addition of the above-mentioned reagents to aldehyde **20** had to involve a disfavored anti-Felkin−Anh transition state.[13,37,38] To override the stereochemical bias exerted by the C8 stereocenter in aldehyde **20**, the use of chiral nucleophilic reagents exhibiting high π-facial selectivities had to be considered in this double-asymmetric condensation proceeding in the mismatched manifold.[39] Although its influence was anticipated to contribute to a smaller extent to the stereochemical outcome of nucleophilic additions to aldehyde **20**, it is worth mentioning that, on the basis of Evan's model for 1,3-asymmetric induction, the β-alkoxy-substituted stereocenter (C7) should reinforce the formation of the anti-Felkin diastereomeric adduct of type **I** (*anti* stereochemical relationship between both oxygenated moieties at C7 and C9 in the extended zigzag conformation) (Scheme 7).[40]

The first chain extension attempt was carried out by using an aldol condensation, and the methodology developed by Paterson, based on the use of the boron

(33) Other mechanisms were also discussed in ref 18a in order to explain the stereoselectivities of mercury(II)-mediated opening of cyclopropanes by internal nucleophiles. These processes were assumed to be under kinetic control,[18a] but this was not verified in the particular case of substrates **12b** and **12c**. Indeed, reversibility has already been observed in case of alkenes, see: Harding, K. E.; Marman, T. H. *J. Org. Chem.* **1984**, *49*, 2838.

(34) Balkrishna, B. S.; Childers, W. E., Jr.; Pinnick, H. W. *Tetrahedron* **1981**, *37*, 2091.

(35) Hashimoto, N.; Aoyama, T.; Shioiri, T. *Chem. Pharm. Bull.* **1981**, *29*, 1475.

(36) Dess, D. B.; Martin, J. C. *J. Am. Chem. Soc.* **1991**, *113*, 7277.

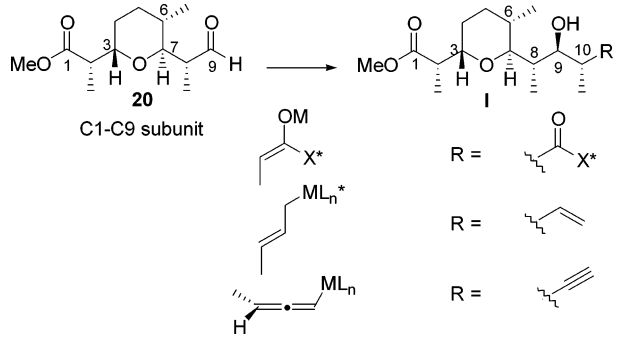
(37) For a recent review, see: Mengel, A.; Reiser, O. *Chem. Rev.* **1999**, *99*, 1191.

(38) Roush, W. R. *J. Org. Chem.* **1991**, *56*, 4151 and references herein.

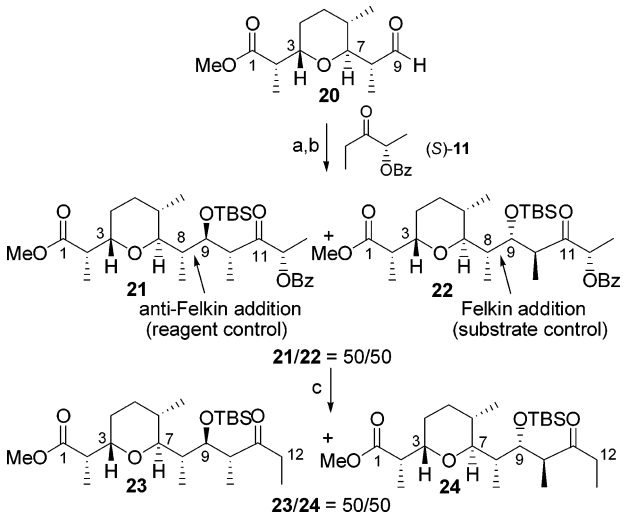
(39) Masamune, S.; Choy, W.; Petersen, J. S.; Sita, L. R. *Angew. Chem., Int. Ed. Engl.* **1985**, *24*, 1.

(40) (a) Evans, D. A.; Duffy, J. L.; Dart, M. J. *Tetrahedron Lett.* **1994**, *35*, 8537. (b) Evans, D. A.; Dart, M. J.; Duffy, J. L.; Yang, M. G.; Livingston, A. B. *J. Am. Chem. Soc.* **1995**, *117*, 6619. (c) Evans, D. A.; Dart, M. J.; Duffy, J. L.; Yang, M. G. *J. Am. Chem. Soc.* **1996**, *118*, 4322.

SCHEME 7. Carbon Chain Extension of the C1−C9 Subunit



SCHEME 8. Addition of a Chiral Enolate to Aldehyde 20[a]



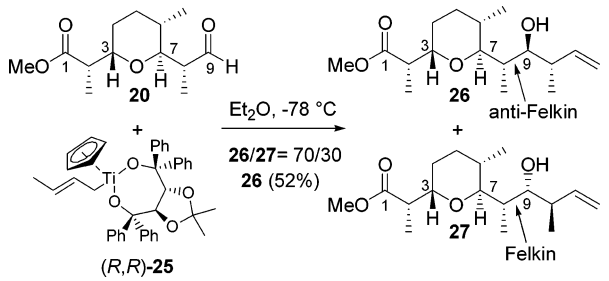
[a] Reagents and conditions: (a) (*S*)-**11**, *c*-Hex_2BCl, $EtNMe_2$, Et_2O, 0 °C then add **20**, −78 to −23 °C; (b) TBSOTf, 2,6-lutidine, CH_2Cl_2, −78 °C (41% from **20**); (c) SmI_2, THF/MeOH, 0 °C (93%).

enolates generated from chiral ethyl ketones (derived from lactic esters), was selected.[31] However, the addition of the (*E*)-boron enolate derived from the ethyl ketone (*S*)-**11** to aldehyde **20** proceeded in an essentially stereorandom fashion. Indeed, after silylation of the hydroxyl group at C9, a 50/50 diastereomeric mixture of ketones **21** and **22** was obtained (41%) and subsequent reductive removal of the benzoyloxy group was achieved by treatment with samarium diiodide in THF/MeOH[31] to give an inseparable 50/50 diastereomeric mixture of ethyl ketones **23** and **24** (93%) (Scheme 8). The relative configuration of these two diastereomeric ethyl ketones was assigned by comparison to **23** prepared by another route (vide infra).

Therefore, aldehyde **20** exhibited an underestimated propensity to bias the nucleophilic additions into the Felkin−Anh mode and the facial selectivity displayed by the chiral enolate derived from ethyl ketone (*S*)-**11** was not high enough to override the influence of the aldehyde C8 stereocenter.

Consequently, a more powerful face-selective reagent had to be chosen, and we next envisaged the addition of a chiral crotylmetal reagent. The Hafner−Duthaler crotyltitanium reagents bearing a chiral TADDOL ligand have been demonstrated to be highly face-selective

SCHEME 9. Addition of a Chiral Crotyltitanium Reagent to Aldehyde 20



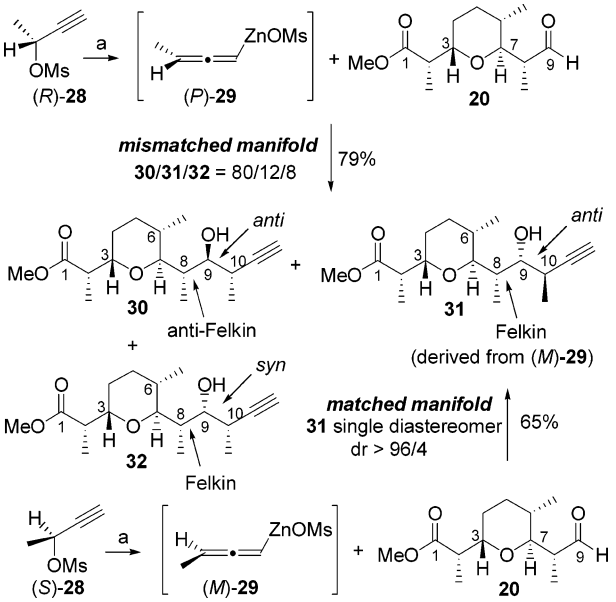
reagents, capable of overriding substrate control in numerous situations wherein chiral aldehydes have been used.[41] However, when the (*E*)-chiral crotyltitanium reagent (*R*,*R*)-**25** which is known to direct the nucleophilic addition to the *Si* face of aldehydes[41] was condensed with aldehyde **20**, a 70/30 mixture of two separable diastereomeric homoallylic alcohols **26** and **27** was obtained and the major diastereomer **26** was isolated in 52% yield. Both homoallylic alcohols **26** and **27** necessarily exhibit an *anti*-relationship between the methyl group at C10 and the hydroxyl group at C9, due to the involvment of an (*E*)-crotylmetal reagent. Moreover, the major diastereomeric homoallylic alcohol **26**, which was anticipated to result from an anti-Felkin addition controlled by the face-selective crotyltitanium complex (*R*,*R*)-**25**, should possess the required configurations at C8−C10. The minor diastereomeric homoallylic alcohol **27** would in turn result from a substrate-directed Felkin−Anh addition process (Scheme 9). These stereochemical assignments were confirmed by the synthesis of these diastereomeric homoallylic alcohols according to another strategy (vide infra).

Although the diastereoselectivity was improved in favor of the diastereomeric homoallylic alcohol **26** having the requisite *anti*,*anti*-relative configuration at C8−C10, another class of chiral nucleophiles, the allenylzinc reagents, was tested since these reagents were demonstrated to undergo highly diastereoselective reagent-controlled additions to chiral aldehydes. Thus, the chiral allenylzinc reagent (*P*)-**29** was generated in situ from the optically enriched propargylic mesylate (*R*)-**28** (cat. $Pd(OAc)_2$, cat. PPh_3, Et_2Zn),[42] and its addition to aldehyde **20** proceeded in the mismatched manifold to afford a diastereomeric mixture of three homopropargylic alcohols **30**, **31**, and **32** in an 80/12/8 ratio. These diastereomers were separated by flash chromatography and respectively isolated in 63%, 9%, and 7% yields (combined yield 79%) (Scheme 10). To unambiguously assign the configuration of these three diastereomeric homopropargylic alcohols, the allenylzinc reagent (*M*)-**29** derived from the enantiomeric propargylic mesylate (*S*)-**28** was also reacted with aldehyde **20**. This reaction, which now proceeded in the matched manifold, afforded the homopropargylic alcohol **31** as a single diastereomer in 65% isolated yield (Scheme 10).

(41) (a) Hafner, A.; Duthaler, R. O.; Marti, R.; Rihs, G.; Rothe-Streit, P.; Schwarzenbach, F. *J. Am. Chem. Soc.* **1992**, *114*, 2321. (b) Cossy, J.; BouzBouz, S.; Pradaux, F.; Willis, C.; Bellosta, V. *Synlett* **2002**, 1595. (c) BouzBouz, S.; Cossy, J. *Org. Lett.* **2001**, *3*, 3995.

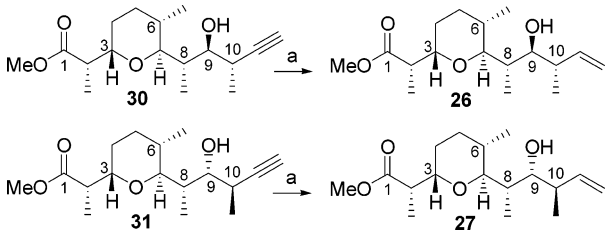
(42) (a) Marshall, J. A.; Adams, N. D. *J. Org. Chem.* **1999**, *64*, 5201. (b) Marshall, J. A. *Chem. Rev.* **2000**, *100*, 3163.

SCHEME 10. Addition of Chiral Allenylzinc Reagents to Aldehyde 20[a]



[a] Reagents and conditions: cat. $Pd(OAc)_2$, cat. PPh_3, Et_2Zn, THF, −30 °C.

SCHEME 11 [a]



[a] Reagents and conditions: H_2 (1 atm), cat. $Pd/BaSO_4$, quinoline, toluene, rt (**26**: 93%, **27**: 48%).

Moreover, partial hydrogenation of the triple bond of the diastereomeric homopropargylic alcohols **30** and **31** respectively afforded the homoallylic alcohols **26** (93%) and **27** (48%) (Scheme 11). Since these last two compounds had been previously synthesized by addition of a chiral (*E*)-crotyltitanium reagent to aldehyde **20** (Scheme 9), this result demonstrated that alcohols **26**, **27**, **30**, and **31** all shared the same C9−C10 *anti* relative configuration. Consequently, the C9−C10 relative configuration in the minor diastereomeric homopropargylic alcohol **32** was necessarily *syn*. To explain the formation of the minor diastereomer **31**, having a C8−C9 *syn* relative configuration, the formation of the enantiomeric allenylzinc reagent (*M*)-**29** has to be considered as a consequence of the racemization of the intermediate allenylpalladium species.[43]

These results were in agreement with those reported by Marshall for double-asymmetric nucleophilic additions of chiral allenylzincs to simple α-methyl-*β*-alkoxy-substituted aldehydes.[44] However, the presence of the bulky trisubstituted tetrahydropyran substituent (C1−C7) may be responsible for the difficulties of aldehyde **20** to accommodate nucleophilic additions through an anti-Felkin transition state. The influence of the *β*-oxygenated substituted stereocenter (C7)[40] in aldehyde **20** appeared to be negligible or was not able to compensate the stereochemical bias exerted by the C8 stereocenter which seemed to be difficult to override completely.[45]

Though the undesired diastereomeric homopropargylic alcohols *syn*,*anti*-**31** and *syn*,*syn*-**32** accounted for one-fifth of the total products, the major diastereomeric homopropargylic alcohol **30** formed during the course of the allenylzinc addition, which possesses the required absolute configurations at C9 and C10 for the synthesis of zincophorin, was nevertheless isolated in acceptable yield (63%), and partially hydrogenated to the homoallylic alcohol **26** (93%).

The synthesis of the C1−C12 subunit of zincophorin was then pursued from the homoallylic alcohol **26**, and the hydroxyl group at C9 was protected as a TBS ether **33** (87%). After dihydroxylation of the double bond and oxidative cleavage of the 1,2-diol with sodium periodate, the resulting aldehyde **34** was treated with an excess of lithium diethylcuprate (prepared from etheral ethyllithium−lithium bromide complex and copper iodide) to chemoselectively produce a secondary alcohol[46] which was oxidized with Dess−Martin periodinane (DMP)[36] to afford ethyl ketone **23**. These latter four steps proceeded extremely cleanly, and it was not necessary to purify any of the intermediates. Under these conditions, the ethyl ketone **23** which constitutes the C1−C12 subunit of zincophorin was obtained in 68% yield from the silyl ether **33** (Scheme 12).

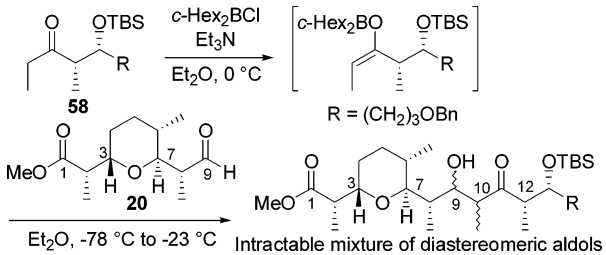
The preparation of the C13−C25 subunit, which contains three of the thirteen asymmetric carbons of zincophorin (C18, C19, and C22) as well as two double bonds of (*E*) configuration (C16−C17 and C20−C21), was next examined.

In our retrosynthetic analysis of the aldehyde of type **C**, the formation of the C16−C17 disubstituted (*E*)-alkene was envisaged by performing the *anti*-reduction of the carbon−carbon triple bond in a disubstituted alkyne of

(43) Allenylpalladium complexes have been shown to be configurationally labile, especially in the presence of zerovalent palladium catalysts, whereas the configurational stability of allenylzinc reagents has been clearly demonstrated: (a) Poisson, J.-F.; Normant, J.-F. *J. Am. Chem. Soc.* **2001**, *123*, 4639. (b) Poisson, J.-F.; Chemla, F.; Normant, J.-F. *Synlett* **2001**, 305.

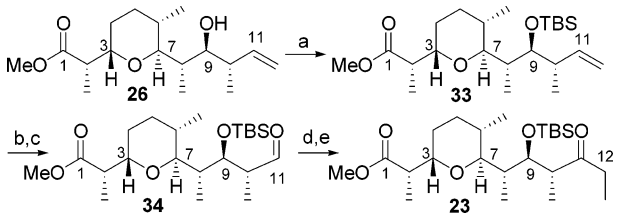
(44) (a) Marshall, J. A.; Schaaf, G. M. *J. Org. Chem.* **2001**, *66*, 7825. (b) Marshall, J. A.; Bourbeau, M. P. *J. Org. Chem.* **2002**, *67*, 2751.

(45) Other face-selective nucleophiles could have been considered but were not tested. It is also worth indicating that an alternative retrosynthetic analysis of zincophorin based on a disconnection at the C9−C10 bond had also been envisaged. However, a model study revealed a complete absence of diastereoselectivity in the aldol condensation of the (*E*)-boron enolate derived from ethyl ketone **58**, a simplified surrogate for the C10−C25 fragment of zincophorin, with aldehyde **20**.



(46) Posner, G. H.; Whitten, C. E.; McFarland, P. E. *J. Org. Chem.* **1972**, *94*, 5106.

SCHEME 12. Synthesis of the C1−C12 Subunit of Zincophorin[a]



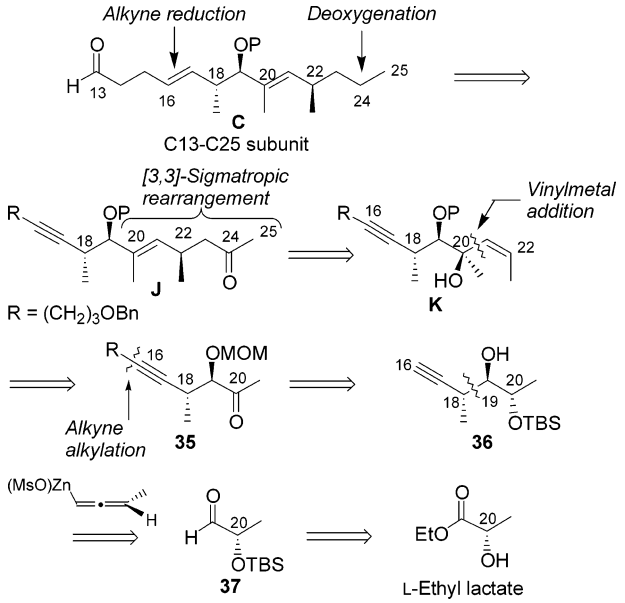
[a] Reagents and conditions: (a) TBSOTf, 2,6-lutidine, CH_2Cl_2, −78 °C (87%); (b) cat. OsO_4, NMO, acetone/H_2O; (c) $NaIO_4$, THF/H_2O; (d) Et_2CuLi [from 2EtLi·LiBr + CuI, Et_2O, −40 °C], Et_2O, −78 °C; (e) DMP, Pyr, CH_2Cl_2 (68% from **33**).

type **J**. The other assumption was to take advantage of a [3,3]-sigmatropic rearrangement in order to create the C20−C21 trisubstituted (*E*)-alkene and control the absolute configuration of the asymmetric carbon at C22.[47,48] Accordingly, subsequent deoxygenation of the carbonyl group at C24 would then be required in order to obtain the C13−C25 subunit **C**. The requisite [3,3]-sigmatropic rearangement precursor would therefore be an appropriate derivative of the tertiary allylic alcohol of type **K**. Since the absolute configuration at C22 would result from a chirality transfer arising during the [3,3]-sigmatropic rearrangement, the choice of the configuration of the tertiary alcohol at C20 as well as the configuration of the propenyl unit were crucial issues to consider in advance.[47,48] Moreover, the propenyl moiety could be introduced by nucleophilic addition of a vinylmetal derivative to the corresponding methyl ketone **35**. Due to its excellent coordinating ability, the OMOM protecting group was chosen for the hydroxyl at C19 so that nucleophilic additions to the carbonyl group of methyl ketone **35** may proceed according to the Cram-chelated model.[49] On the basis of literature results concerning the stereoselectivity of [3,3]-sigmatropic rearrangements in the acyclic series, this choice entailed the addition of a propenylmetal of (*Z*) configuration.[47,48]

Methyl ketone **35** could be synthesized from the known homopropargylic alcohol **36** in which the C13−C15 three carbon unit (R = $(CH_2)_3OBn$) would be introduced by alkylation of the terminal alkyne moiety and the configuration of the two stereocenters C18 and C19 controlled by the nucleophilic addition of a chiral allenylzinc reagent to aldehyde **37**, easily prepared from L-ethyl lactate (Scheme 13).[50]

Protection of the hydroxyl group of L-ethyl lactate as a *tert*-butyldimethylsilyl ether gave **38** (85%),[51] and subsequent reduction with Dibal-H in ether at −40 °C afforded the sensitive aldehyde **37** (100%), which was directly engaged in the next step. Treatment of this

SCHEME 13. Retrosynthetic Analysis of the C13−C25 Subunit



aldehyde with the chiral allenyl zinc (*M*)-**29**, generated in situ from the propargylic mesylate (*S*)-**28**, afforded the homopropargylic alcohol **36** with high diastereoselectivity (dr > 96/4, 75%).[50] Indeed, this double-asymmetric condensation of the chiral allenylzinc (*M*)-**29** proceeded in the matched manifold with respect to the stereocenter of aldehyde **37**.

The hydroxyl group at C19 was protected as a methoxymethyl ether **39** (88%), and the terminal alkyne was deprotonated with *n*-BuLi followed by alkylation of the resulting lithium acetylide with 1-benzyloxy-3-bromopropane, in the presence of HMPA as a polar cosolvent, to provide the disubstituted alkyne **40** (92%).[52] The silyl protecting group of the hydroxyl at C20 was removed with *n*-Bu_4NF in THF, and the resulting secondary alcohol **41** was directly oxidized with Dess−Martin periodinane[36] in the presence of pyridine to afford methyl ketone **35** (92% from **40**). The addition of (*Z*)-prop-1-enylmagnesium bromide, prepared by transmetalation of the readily available (*Z*)-prop-1-enyllithium with an excess of magnesium bromide etherate, to the methyl ketone **35** afforded a diastereomeric mixture of the tertiary alcohols **42** and **42′** (93%, **42**/**42′** = 9/1) which were not separated at this stage. The relative configuration of the major diastereomer, depicted as **42**, was

(47) Ziegler, F. E. *Chem. Rev.* **1988**, *88*, 1423.

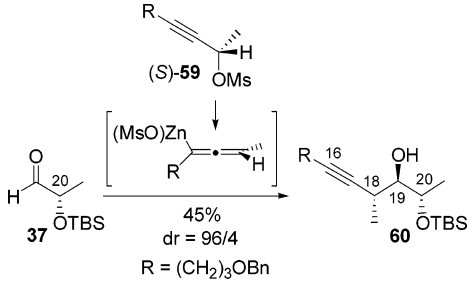
(48) Frauenrath, H. In *Houben Weyl (Methods of Organic Chemistry), Stereoselective Synthesis*; Helmchen, G., Hoffmann, R. W., Mulzer, J., Schaumann, E., Eds.; Thieme Verlag: Stuttgart, 1995; Vol. E21d, pp 3301−3756.

(49) Generally, Cram-chelated additions of organometallic reagents to carbonyl derivatives proceed with substantially higher diastereoselectivites compared to the Felkin−Anh mode: Reetz, M. T. *Acc. Chem. Res.* **1993**, *26*, 462.

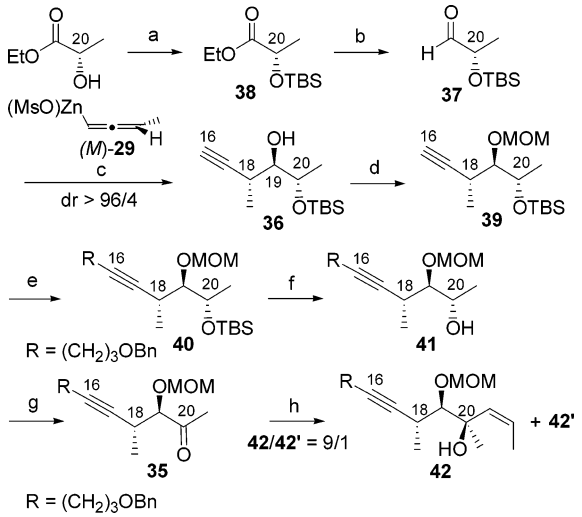
(50) (a) Marshall, J. A.; Chobanian, H. R. *J. Org. Chem.* **2000**, *65*, 8357. (b) Marshall, J. A.; Xie, S. *J. Org. Chem.* **1995**, *60*, 7230.

(51) (a) Massad, S. K.; Hawkins, L. D.; Baker, D. C. *J. Org. Chem.* **1983**, *48*, 5180. (b) Procopiou, P. A.; Baugh, S. P. D.; Falck, S. S.; Inglis, G. G. A. *J. Org. Chem.* **1998**, *63*, 2342.

(52) A more convergent approach involving the addition of the chiral allenylzinc, derived from the propargylic mesylate (*S*)-**59** bearing a disubstituted triple bond, to aldehyde **37** was also investigated. However, this reaction was not reproducible and afforded at best the homopropagylic alcohol **60** in 45% yield (dr ≥ 96/4).



SCHEME 14 [a]



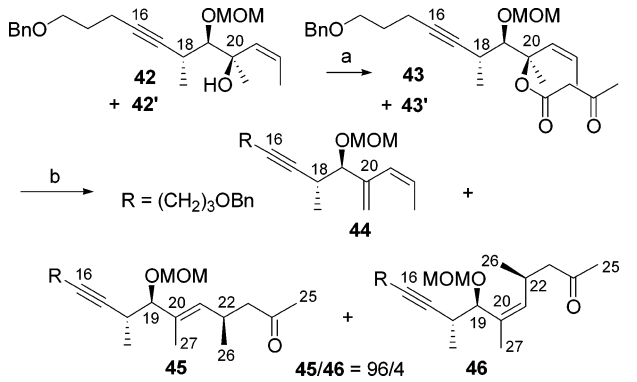
[a] Reagents and conditions: (a) TBSCl, imidazole, THF (85%); (b) Dibal-H, Et_2O, −40 °C (100%); (c) (*S*)-**28**, cat. $Pd(OAc)_2$, cat. PPh_3, Et_2Zn, THF, −20 °C (75%); (d) MOMCl, *i*-Pr_2NEt, CH_2Cl_2 (88%); (e) *n*-BuLi, THF, −78 °C then $BnO(CH_2)_3Br$, HMPA, −78 °C to rt (92%); (f) *n*-Bu_4NF, THF; (g) DMP, Pyr, CH_2Cl_2 (92% from **40**); (h) ((*Z*)-prop-1-enyl)MgBr [from ((*Z*)-prop-1-enyl)Li and $MgBr_2 \cdot OEt_2$, THF/Et_2O, 0 °C to rt], −78 °C (93%).

reasonably attributed on the basis of the Cram-chelate model, due to the presence of the coordinating OMOM group at the α-position of the carbonyl group (Scheme 14).[49]

The next crucial step in the synthesis of the C13−C25 fragment involved the [3,3]-sigmatropic rearrangement of an appropriate substituted vinylic ether derived from the tertiary alcohol **42**. This suitable vinyl ether derivative has to be generated under sufficiently mild conditions due to the propensity of tertiary alcohols to dehydrate under acidic or thermal conditions.[47,48] Since ketene silyl acetals can be generated under mild conditions, the most attractive option was to acetylate the tertiary allylic alcohol **42** in order to perform a subsequent Ireland-Claisen rearrangement.[47,48] However all attempts to acetylate the tertiary alcohols **42/42′** under a variety of conditions failed.[53] By contrast, the diastereomeric mixture of the tertiary alcohols **42** and **42′** (9/1 ratio) smoothly reacted with diketene in the presence of a catalytic amount of DMAP to afford the tertiary acetoacetates **43** and **43′** (9/1 ratio). The major diastereomer **43** was easily separated from the corresponding epimeric acetoacetate at C20 **43′** by flash chromatography and isolated in 88% yield. This successful derivatization of the tertiary alcohol **42** in the form of the β-ketoester **43** led us to rely on a Carroll−Claisen rearrangement.[54]

Initial attempts to perform the Carroll rearrangement of the β-ketoester **43** met with little success. Rearrangement under thermal conditions (xylenes, reflux) afforded an intractable mixture of products, whereas milder

SCHEME 15. Carroll−Claisen Rearrangement of 43[a]



[a] Reagents and conditions: (a) diketene, cat. DMAP, THF, rt (**43**: 88%, **43′**: 8%); (b) adsorption on Al_2O_3, 60 °C (**44**: 4−10%; **45** + **46**: 64−72%).

reaction conditions relying on the formation of the β-ketoester dianion (LDA (2.5−3 equiv), THF, reflux)[55−57] only led to traces of the desired product and instead the conjugated diene **44**, presumably resulting from an intramolecular elimination of acetoacetate, was obtained in 20% yield. Similarly, the use of a Pd(0) catalytic system (cat. $Pd(OAc)_2$, NaH, *t*-BuOH, reflux) led only to traces of the diene **44** resulting from β-hydride elimination from the intermediate π-allylic Pd(0) complex.[58]

Fortunately, it was found that the adsorption of the tertiary allylic acetoacetate **43** on neutral alumina, followed by heating the resulting dry powder overnight at 60 °C was successful at promoting the Carroll−Claisen rearrangement.[59] Under these conditions, the two isomeric methyl ketones **45** and **46** were obtained in satisfactory yield (64−72%, depending on the reaction scale) and the stereoselectivity was high (**45**/**46** = 96/4). It is noteworthy that the intramolecular elimination reaction of the β-ketoester **43** leading to the conjugated diene **44** (4−10%) was not a serious competing side reaction under these conditions (Scheme 15).

The two stereoisomeric ketones **45** and **46** were separated by flash chromatography. The (*E*)- and (*Z*)- configuration of the double bond in ketones **45** and **46** respectively, was deduced from the examination of the chemical shifts of C19 and the vinylic methyl group (C27) by ^{13}C NMR.[60] The relative configuration at C22 was first assigned on the basis of the well-known propensity of

(53) The use of acetic anhydride in the presence of nucleophilic catalysts such as DMAP turned out to be inefficient since no reaction was observed at rt, whereas moderate heating of the reaction mixture resulted in extensive degradation. Moreover, conditions involving Lewis acids induced the removal of the MOM protecting group and the formation of numerous side products.

(54) (a) Carroll, M. F. *J. Chem. Soc.* **1940**, 704. (b) Carroll, M. F. *J. Chem. Soc.* **1940**, 1266. (c) Carroll, M. F. *J. Chem. Soc.* **1941**, 507.

(55) Wilson, S. R.; Price, M. F. *J. Org. Chem.* **1984**, *49*, 722.

(56) (a) Gilbert, J. C.; Kelly, T. A. *Tetrahedron* **1988**, *44*, 7587. (b) Snider, B. B.; Beal, R. B. *J. Org. Chem.* **1988**, *53*, 4508. (c) Echavarren, A. M.; de Mendoza, J.; Prados, P.; Zapata, A. *Tetrahedron Lett.* **1991**, *32*, 6421. (d) Ouvrard, N.; Rodriguez, J.; Santelli, M. *Tetrahedron Lett.* **1993**, *34*, 1149. (e) Genus, J. F.; Peters, D. D.; Ding, J.-F.; Bryson, T. A. *Synlett* **1994**, 209. (g) Hatcher, M. A.; Posner, G. H. *Tetrahedron Lett.* **2002**, *43*, 5009.

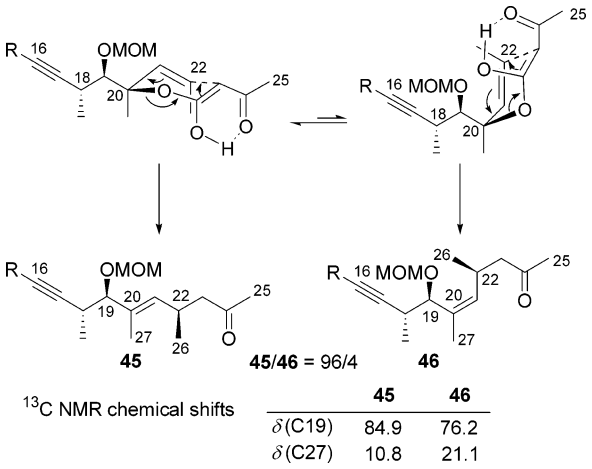
(57) For an asymmetric version of the Carroll-Claisen rearrangement, see: Enders, D.; Knopp, M.; Runsink, J.; Raabe, G. *Angew. Chem, Int. Ed. Engl.* **1995**, *34*, 2278.

(58) Tsuji, J.; Yamada, T.; Minami, I.; Yuhara, M.; Nisar, M.; Shimizu, I. *J. Org. Chem.* **1987**, *52*, 2988.

(59) Pogrebnoi, S. I.; Kalyan, Y. B.; Krimer, M. Z.; Smit, W. A. *Tetrahedron Lett.* **1987**, *28*, 4893.

(60) Kalinowski, H.-O.; Berger, S.; Braun, S. In *Carbon-13 NMR Spectroscopy;* J. Wiley & Sons: New York, 1988: The γ-gauche effect exerted by the *cis*-olefinic substituent (C22−C25) resulted in an upfield shift of the C27 methyl group in the (*E*)-isomer **45**, whereas this upfield shift was conversely observed for C19 in the (*Z*)-isomer **46**.

SCHEME 16. Stereoselectivity of the Carroll−Claisen Rearrangement of 43

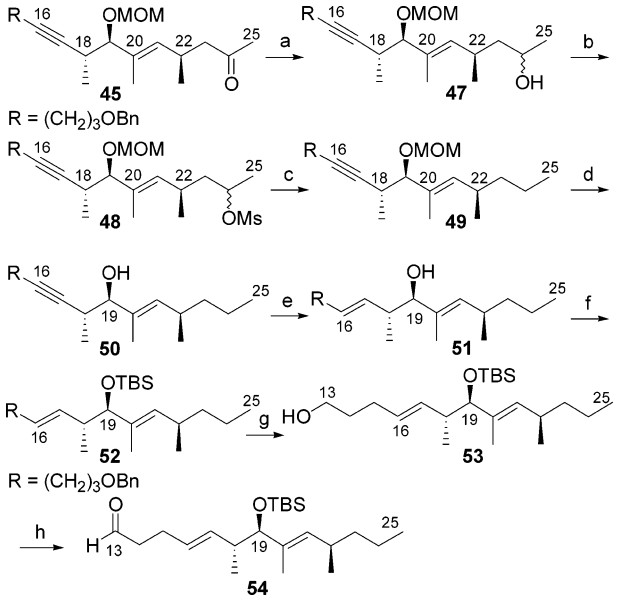


[3,3]-sigmatropic rearrangements to proceed (in the acyclic series) through a chairlike transition state.[47,48] Two conformers could be distinguished in which either the branched C19−C13 chain or the methyl group may occupy an axial position. Since there was an appreciable difference of steric bulk between both substituents, the branched chain at C20 was expected to preferentially occupy the less congested equatorial position, and the rearrangement would lead to the major methyl ketone **45** having a double bond of (*E*)-configuration and a C22 stereocenter of (*R*)-configuration. Conversely, rearrangement of the alternative conformer would lead to the minor stereoisomer **46** having a double bond of (*Z*)-configuration and an (*S*) configuration at C22 (Scheme 16).[61]

The synthesis of the C13−C25 fragment was then pursued from the γ,δ-unsaturated ketone **45**, which was reduced with Dibal-H in ether at −78 °C to afford the secondary alcohol **47** (55/45 diasteromeric mixture, 98%). This alcohol was converted to the corresponding mesylate **48** which was reduced with lithium aluminum hydride in refluxing THF to afford the C24 deoxygenated product **49** (88% yield from **47**) (Scheme 17).[62,63] Having removed the carbonyl group at C24, the next crucial step in the elaboration of the C13−C25 subunit of zincophorin was the stereoselective reduction of the triple bond in order to elaborate the C16−C17 disubstituted double bond of (*E*)-configuration. However, in compound **49**, the secondary alcohol moiety at C19 was protected as a methoxymethyl ether and its deprotection at a later stage in the synthesis of zincophorin turned out to be a difficult task.[64,65]

With the aim of replacing the MOM protecting group at C19 by a TBS group, the deprotection of the disubsti-

SCHEME 17. Synthesis of the C13−C25 Subunit of Zincophorin[a]



[a] Reagents and conditions: (a) DIBAL-H, Et_2O, −78 °C (98%); (b) MsCl, *i*-Pr_2NEt, CH_2Cl_2, 0 °C; (c) $LiAlH_4$, THF, reflux (88% from **47**); (d) *p*-TsOH, MeOH, rt (85%); (e) $LiAlH_4$, THF, reflux (61%); (f) TBSOTf, 2,6-lutidine, CH_2Cl_2, −78 °C; (g) Li, NH_3 (l), THF/*t*-BuOH (75% from **51**); (h) DMP, Pyr, CH_2Cl_2 (86%).

tuted alkyne **49** was first investigated. Thus, the secondary alcohol moiety in compound **49** was slowly but efficiently deprotected by treatment with a stoichiometric amount of *p*-toluenesulfonic acid in methanol at room temperature for 4 days to afford the corresponding homopropargylic alcohol **50** (85%). As the dissolving metal reduction of the triple bond failed after protection of the secondary alcohol at C19 in compound **50** as a *tert*-butyldimethylsilyl ether,[66,67] it was decided to take advantage of the presence of the free hydroxyl group at

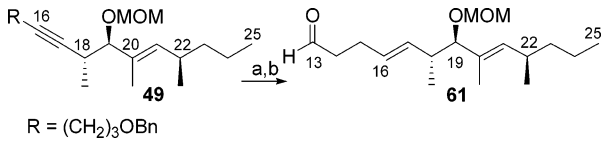
(61) The validity of this stereochemical assignment was confirmed on a simpler model substrate: Medana, S.; Meyer, C.; Cossy, J. Unpublished results. See the Supporting Information for details.

(62) This two-step sequence was preferred compared to a one-pot procedure involving the formation of the tosylhydrazone derived from methyl ketone **45** followed by in situ reduction with sodium cyanoborohydride, which afforded the corresponding deoxygenated product **49** in only 16% isolated yield: Hutchins, R. O.; Maryanoff, B. E.; Molewski, C. A. *J. Am. Chem. Soc.* **1971**, *93*, 1793.

(63) A radical deoxygenation (*n*-Bu_3SnH, cat. AIBN, toluene, reflux) of the thiocarbonate derived from the secondary alcohol **47** (PhOC(S)-Cl, pyridine, 1,2-dichloroethane, reflux) was also satisfactory and afforded the C24 deoxygenated product **49** in 76% yield.

(64) There are several literature reports dealing with the difficulties associated with the removal of the MOM protecting group in the case of highly functionalized substrates; see: (a) Kocienski, P. J. *Protecting Groups*; Georg Thieme Verlag: New York, 1994. (b) Greene, T. W.; Wuts, P. G. M. *Protective Groups in Organic Synthesis*; J. Wiley & Sons: New York, 1999.

(65) The synthesis of the C13−C25 subunit aldehyde **61** having the hydroxyl group at C19 protected as a MOM ether was first completed from **49**. Although its subsequent aldol coupling with ethyl ketone **23** was successful, it turned out impossible to remove the MOM group later in the synthesis with decent chemical yield (key: (a) Li, NH_3 (l), THF/*t*-BuOH (4:1), −33 °C (75%); (b) DMP, Pyr, CH_2Cl_2 (82%)).



(66) The protecting group of the homopropargylic hydroxyl at C19 seemed to have a marked influence on the dissolving-metal reduction of the triple bond. The reduction of the alkyne **49** having a MOM protecting group efficiently occurred albeit slowly.[65] When the MOM group was replaced by a TBS group, the triple bond failed to be reduced in the corresponding substrate and only the debenzylation of the hydroxyl group at C13 was observed. By contrast, compound **50** having the alcohol moiety unprotected at C19 underwent both reactions at a rapid rate and overreduction of the triple bond to the corresponding alkane was also observed. The different solubilities of these compounds in liquid ammonia may be in part responsible for these differences.[67]

(67) Brandsma, L.; Nieuwenhuizen, W. F.; Zwikker, J. W.; Mäeorg, U. *Eur. J. Org. Chem.* **1999**, 775, and references therein.

the homopropargylic position and reduce the triple bond by using lithium aluminum hydride. Indeed, the secondary alcohol **50** was slowly but efficiently hydroaluminated with $LiAlH_4$ in refluxing THF and the (*E*)-homoallylic alcohol **51** was obtained in 61% unoptimized yield. Protection of the hydroxyl group at C19 as a *tert*-butyldimethylsilyl ether afforded compound **52**, which was subjected to a Birch reduction at −78 °C. The resulting primary alcohol **53** (75% from **51**) was then oxidized with Dess−Martin periodinane (DMP)[36] to afford aldehyde **54** (86%), which constitutes the C13−C25 subunit of zincophorin having the secondary alcohol moiety at C19 protected as a *tert*-butyldimethylsilyl ether (Scheme 17).

Having synthesized ethyl ketone **23** (C1−C12 subunit) and aldehyde **54** (C13−C25 subunit), their coupling was examined by using an aldol reaction, in agreement with our retrosynthetic analysis (Scheme 4).

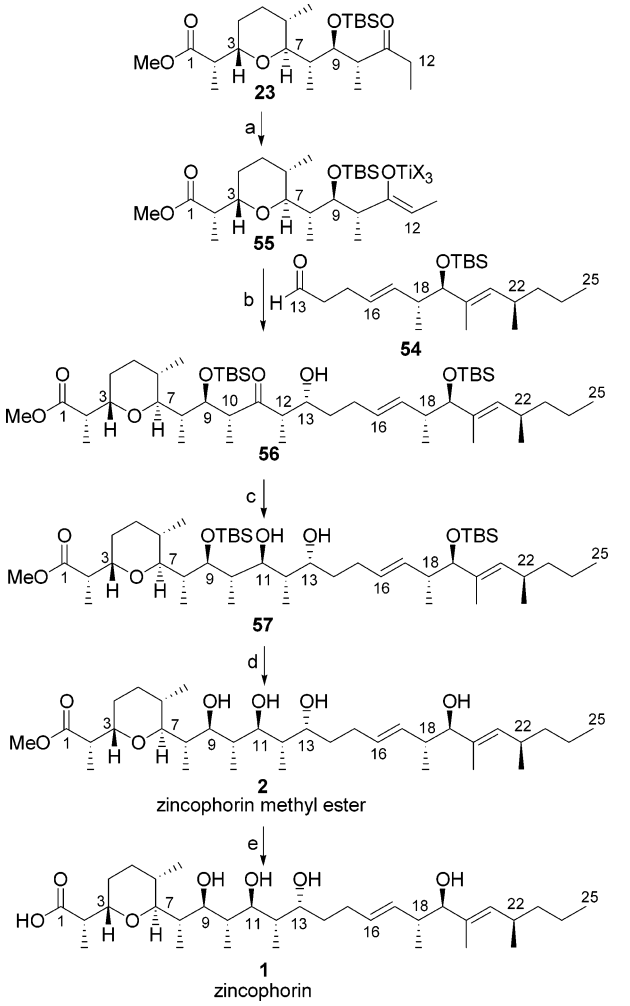
Due to the C12−C13 *syn* relative configuration, it was necessary to achieve the addition of a (*Z*)-enolate derived from ethyl ketone **23** to aldehyde **54**. Thus, the (*Z*)-titanium enolate **55** derived from ethyl ketone **23** was generated by treatment with titanium tetrachloride and Hünig's base in dichloromethane at −78 °C.[17] Reaction with aldehyde **54** afforded the corresponding aldol **56** (70%) with high diastereoselectivity (dr > 96/4, single diastereomer detected by ^{1}H NMR). As mentioned previously, there were detailed literature precedents on these aldol reactions supporting the indicated stereochemical outcome (*syn* relationship between the methyl groups at C10 and C12) (Scheme 18).[17] The completion of the total synthesis of zincophorin methyl ester **2** was then investigated. The diastereoselective reduction of the carbonyl group at C11 was efficiently and simply carried out by using sodium borohydride in methanol[68] and the corresponding diol **57** was directly treated with HF·Pyridine in THF in order to deprotect both alcohol functionalities at C9 and C19. Under these conditions, zincophorin methyl ester **2** was obtained in 66% yield from the aldol **56** (Scheme 18).

The analytical and spectroscopic data of zincophorin methyl ester **2** thus obtained, including R_f in two solvent systems,[6] IR[6,8] and ^{1}H NMR spectra[8] as well as the optical rotation ($[\alpha]_D$ +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, $CHCl_3$),[8] authentic sample: $[\alpha]_D$ +20.9 (*c* 2.0, $CHCl_3$)[1,6]).

In the previously reported total synthesis by Danishefsky, zincophorin was obtained from its methyl ester by saponification. However, due to the difficulties associated with its purification, zincophorin was esterified by treatment with etheral diazomethane and converted to the methyl ester **2**.[8]

We therefore attempted to carry out the saponification of zincophorin methyl ester **2** with aqueous lithium hydroxide in THF/methanol at 50 °C. Although this reaction proceeded cleanly, attempts to purify zincophorin by chromatography on silica gel led to an undetermined metal-salt of zincophorin, whose ^{1}H NMR spectrum favorably compared with the one recorded for

SCHEME 18. Total Synthesis of Zincophorin and Its Methyl Ester[a]



[a] Reagents and conditions: (a) $TiCl_4$, *i*-Pr_2NEt, CH_2Cl_2, −78 °C; (b) addition of aldehyde **54**, −78 °C, 2 h, (70%, dr > 96/4); (c) $NaBH_4$, MeOH, 0 °C; (d) HF·Pyr, THF, rt, (66% from **56**); (e) LiOH, H_2O/MeOH/THF (1/1/2), 50 °C (see text).

the magnesium salt of zincophorin.[3−5] Treatment of an etheral solution of this salt with an aqueous solution of the disodium salt of EDTA afforded an amorphous solid which was analyzed by ^{1}H and ^{13}C NMR. Despite the presence of traces of structurally unrelated impurities, presumably from organic solvents due to the repeated manipulations of this sample on such scale (8 mg), the spectra of this material were unambiguously in perfect agreement with the literature data reported for zincophorin free acid **1**.[3−5] However, we do not wish to indicate an accurate yield value for this last step.

We have therefore completed the second total synthesis of zincophorin methyl ester (and zincophorin) according to a convergent strategy involving the coupling of the C1−C12 and C13−C25 subunits by using a highly diastereoselective titanium-mediated aldol condensation. The synthesis of the C1−C12 fragment, which was accomplished in 25 steps from allyl diazoacetate with an overall yield of 6%, 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 sub-

(68) The stereochemical outcome of the reduction of the carbonyl group at C11 in aldol **56** was investigated with simpler model substrates. See the Supporting Information for details.

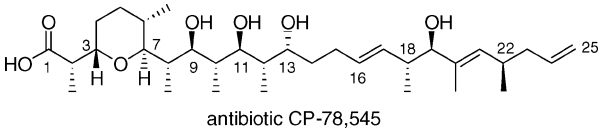


FIGURE 2.

unit was achieved in 18 steps from L-ethyl lactate with an overall yield of 7% and relied on a stereoselective Carroll-Claisen rearrangement of a tertiary allylic acetoacetate. This strategy, which entailed the intermediacy of a compound functionalized at C24 by a carbonyl group, should be also particularly well-suited for the total synthesis of antibitiotic CP-78,545. This natural ionophore is the C24−C25-dehydro analogue of zincophorin which was isolated by Pfizer from modified strains of *Streptomyces* (Figure 2).[69]

Experimental Section

Synthesis of the C1−C12 Subunit of Zincophorin. (1*S*,5*R*)-3-Oxabicyclo[3.1.0]hexan-2-one (3).[26] To a solution of Doyle's catalyst Rh_2((5*R*)-MEPY)$_4$ (56 mg, 0.061 mmol, 0.001 equiv) in refluxing CH_2Cl_2 (150 mL) was added, over a period of 30 h, a solution of allyl diazoacetate (7.38 g, 58.5 mmol) in CH_2Cl_2 (350 mL). The solvent was removed by distillation at atmospheric pressure, and the crude material was purified by flash chromatography (pentane/Et_2O gradient 50/50 to 30/70) to give 5.23 g (91%) of **3** as a pale yellow oil: $[\alpha]^{20}_D$ −65.0 (*c* 1.00, $CHCl_3$) ($[\alpha]^{20}_D$ = +60.2 (*c* 1.01, $CHCl_3$) for the (1*R*,5*S*) enantiomer[26]); IR (neat) 3080, 1770, 1180, 1035, 995, 980, 950, 930 cm^{-1}; ^{1}H NMR δ 4.36 (dd, *J* = 9.4 and 4.8 Hz, 1H), 4.23 (d, *J* = 9.4 Hz, 1H), 2.25 (m, 1H), 2.07 (m, 1H), 1.28 (m, 1H), 0.88 (m, 1H); ^{13}C NMR δ 176.4 (s), 69.4 (t), 17.5 (d), 17.3 (d), 12.2 (t); MS-EI *m*/*z* (relative intensity) 98 ($M^{+\bullet}$, 100), 70 (40), 68 (73), 55 (35), 53 (20).

2-((1*S*,2*R*)-2-{[(*tert*-Butyldiphenylsilyl)oxy]methyl}-cyclopropyl)propan-2-ol (4a). To a solution of methyllithium (28 mL, 1.4 M in Et_2O, 39 mmol, 3.9 equiv) in THF (60 mL) at 0 °C was added dropwise a solution of **3** (1.0 g, 10 mmol) in THF (5 mL). After 30 min, a solution of *tert*-butylchlorodiphenylsilane (3.4 mL, 13 mmol, 1.3 equiv) and imidazole (1.8 g, 27 mmol, 2.7 equiv) in DMF (5 mL) was added dropwise, and 1 h later, the reaction mixture was hydrolyzed with a saturated aqueous solution of NH_4Cl and extracted with petroleum ether/CH_2Cl_2 (9/1). The combined extracts were washed with brine, dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The crude material was purified by flash chromatography (petroleum ether/CH_2Cl_2 90/10) to afford 3.4 g (90%) of **4a** as a colorless oil: $[\alpha]^{20}_D$ = +15.2 (*c* 2.1, $CHCl_3$); IR (film) 3430, 3060, 1110, 1065, 1045, 820, 785, 740, 700 cm^{-1}; ^{1}H NMR δ 7.74−7.68 (m, 4H), 7.42−7.34 (m, 6H), 4.12 (dd, *J* = 11.6 and 6.0 Hz, 1H), 3.69 (dd, *J* = 11.6 and 9.8 Hz, 1H), 3.19 (s, 1H, OH), 1.47 (s, 3H), 1.26 (s, 3H), 1.24−1.06 (m, 2H), 1.06 (s, 9H), 0.65 (m, 1H), 0.39 (m, 1H); ^{13}C NMR δ 135.5 (d, 2C), 134.8 (d, 2C), 133.2 (s), 133.1 (s), 129.7 (d), 129.4 (d), 127.7 (d, 2C), 127.6 (d, 2C), 69.6 (s), 64.9 (t), 31.8 (q), 29.7 (q), 27.9 (d), 26.7 (q, 3C), 19.0 (s), 18.5 (d), 7.5 (t); MS-EI *m*/*z* (relative intensity) 353 (M − Me^+, 1), 311 (M − *t*-Bu^+, 5), 199 (100), 139 (26), 95 (21), 69 (76). Anal. Calcd for $C_{23}H_{32}O_2Si$: C, 74.95; H, 8.75. Found: C, 75.03; H, 8.71.

2-{(1*S*,2*R*)-2-[(Benzyloxy)methyl]cyclopropyl}propan-2-ol (4b). To a solution of methyllithium (28 mL, 1.4 M in Et_2O, 39 mmol, 2.6 equiv) in THF (60 mL) at 0 °C was added dropwise a solution of **3** (1.50 g, 15.3 mmol) in THF (15 mL). After 30 min, the reaction mixture was hydrolyzed with a 50% aqueous solution of NaOH (80 mL) and diluted with toluene (80 mL) and CH_2Cl_2 (15 mL). To the resulting mixture were successively added benzyltriethylammonium chloride (500 mg, 2.20 mmol, 0.14 equiv) and benzyl bromide (2.40 mL, 20.1 mmol, 1.3 equiv), and after 20 h at rt, the reaction mixture was cooled to 0 °C, diluted with water (60 mL), and extracted with ether. The combined organic extracts were dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The crude material was purified by flash chromatography (petroleum ether/EtOAc gradient 93/7 to 80/20) to give 3.0 g (89%) of **4b** as a colorless oil: $[\alpha]^{20}_D$ = +43.9 (*c* 1.4, $CHCl_3$); IR (film) 3420, 1245, 1195, 1175, 1160, 1065, 1025, 950, 920, 835, 745, 700 cm^{-1}; ^{1}H NMR δ 7.35−7.26 (m, 5H), 4.57 (d, *J* = 11.8 Hz, 1H), 4.49 (d, *J* = 11.8 Hz, 1H), 3.95 (dd, *J* = 10.3 and 6.4 Hz, 1H), 3.56 (dd, *J* = 10.3 and 8.8 Hz, 1H), 2.76 (br s, 1H, OH), 1.37 (s, 3H), 1.20 (m, 1H), 1.19 (s, 3H), 1.06 (m, 1H), 0.75 (m, 1H), 0.48 (m, 1H); ^{13}C NMR δ 137.7 (s), 128.4 (d, 2C), 127.9 (d, 2C), 127.7 (d), 72.7 (t), 70.5 (t), 69.4 (s), 31.3 (q), 30.0 (q), 27.7 (d), 16.1 (d), 7.5 (t); MS-EI *m*/*z* (relative intensity) 206 (M − Me^+, 0.1), 111 (M−H_2O−Bn^+, 11), 96 (12), 92 (10), 91 (100). Anal. Calcd for $C_{14}H_{20}O_2$: C, 76.33; H, 9.15. Found: C, 76.16; H, 9.35.

(1*S*,2*R*)-2-{[(*tert*-Butyldiphenylsilyl)oxy]methyl}-1-isopropenylcyclopropane (5a). To a solution of **4a** (4.15 g, 11.3 mmol) in CH_2Cl_2 (200 mL) were added Et_3N (24 mL, 0.17 mol, 15 equiv) and DMAP (1.53 g, 12.5 mmol, 1.1 equiv). The resulting mixture was cooled to 0 °C, and MsCl (9.0 mL, 0.12 mmol, 10 equiv) was added dropwise. After 5 h at 0 °C, the reaction mixture was hydrolyzed with a saturated aqueous solution of NH_4Cl and extracted with ether. The combined extracts were washed with brine, dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The crude material was purified by flash chromatography (petroleum ether/EtOAc 95/5) to give 3.37 g (85%) of **5a** as a colorless oil: $[\alpha]^{20}_D$ +10.7 (*c* 1.0, $CHCl_3$); IR (film) 3070, 1645, 1110, 1065, 820, 740, 720, 700 cm^{-1}; ^{1}H NMR δ 7.71−7.65 (m, 4H), 7.40−7.33 (m, 6H), 4.79 (br s, 1H), 4.51 (br s, 1H), 3.64 (dd, *J* = 10.9 and 5.5 Hz, 1H), 3.41 (dd, *J* = 10.9 and 8.9 Hz, 1H), 1.90 (s, 3H), 1.48 (m, 1H), 1.28 (m, 1H), 1.05 (s, 9H), 0.63 (m, 1H), 0.36 (m, 1H); ^{13}C NMR δ 142.9 (s), 135.6 (d, 4C), 134.1 (s, 2C), 129.4 (d, 2C), 127.5 (d, 4C), 110.4 (t), 63.2 (t), 26.8 (q, 3C), 24.3 (q), 22.9 (d), 19.7 (d), 19.2 (s), 6.5 (t); MS-EI *m*/*z* (relative intensity) 350 ($M^{+\bullet}$, 1), 293 (M − *t*-Bu^+, 73), 251 (60), 237 (45), 225 (50), 199 (100), 183 (44). Anal. Calcd for $C_{23}H_{30}OSi$: C, 78.80; H, 8.63. Found: C, 78.82; H, 8.65.

(1*S*,2*R*)-2-[(Benzyloxy)methyl]-1-isopropenylcyclopropane (5b). This compound was synthesized from **4b** (7.41 g, 33.7 mmol) according to the procedure described for preparation of **5a** from **4a**. Purification by flash chromatography (petroleum ether/EtOAc 95/5) afforded 5.68 g (83%) of **5b** as a colorless oil: $[\alpha]^{20}_D$ +34.3 (*c* 1.1, $CHCl_3$); IR (film) 3050, 1640, 1075, 1025, 885, 735, 695 cm^{-1}; ^{1}H NMR δ 7.37−7.28 (m, 5H), 4.85 (apparent br s, 1H), 4.63 (s, 1H), 4.53 (d, *J* = 12.2 Hz, 1H), 4.48 (d, *J* = 12.2 Hz, 1H), 3.45 (dd, *J* = 9.9 and 6.3 Hz, 1H), 3.30 (dd, *J* = 9.9 and 8.1 Hz, 1H), 1.89 (s, 3H), 1.56 (m, 1H), 1.40 (m, 1H), 0.81 (m, 1H), 0.56 (m, 1H); ^{13}C NMR δ 142.7 (s), 138.6 (s), 128.2 (d, 2C), 127.7 (d, 2C), 127.4 (d), 110.7 (t), 72.8 (t), 69.5 (t), 24.0 (q), 22.6 (d), 17.0 (d), 7.1 (t); MS-EI *m*/*z* (relative intensity) 202 ($M^{+\bullet}$, 0.01), 111 (M − Bn^+, 8), 93 (7), 92 (9), 91 (100), 81 (6), 79 (6), 77 (5), 65 (8), 55 (8). Anal. Calcd for $C_{14}H_{18}O$: C, 83.12; H, 8.97. Found: C, 83.04; H, 9.09.

(2*R*)-2-((1*R*,2*R*)-2-{[(*tert*-Butyldiphenylsilyl)oxy]methyl}-cyclopropyl)propan-1-ol (6a). To a solution of **5a** (971 mg, 2.77 mmol) in THF (5 mL) at −30 °C was added dropwise a solution of BH_3·THF (7.0 mL, 1 M in THF, 7.0 mmol, 2.5 equiv). After 30 min at −30 °C and 2 h at rt, the reaction mixture was cooled to 0 °C and a 3 M aqueous NaOH solution (3 mL) and a 30% aqueous solution of H_2O_2 (3 mL) were successively added dropwise. After 3 h at rt, the resulting mixture was extracted with ether, and the combined extracts were washed with brine, dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The crude material was

(69) Dirlam, J. P.; Belton, A. M.; Chang, S. P.; Cullen, W. P.; Huang, L. H.; Kojima, Y.; Maeda, H.; Nishiyama, S.; Oscarson, J. R.; Sakakibara, T. *J. Antibiot.* **1989**, *42*, 1213.

purified by flash chromatography (pertroleum ether/EtOAc 93/7) to give 927 mg (91%) of **6a** as a colorless oil: $[\alpha]^{20}_D$ +26.5 (*c* 1.2, $CHCl_3$); IR (film) 3450, 3060, 1110, 1080, 1040, 820, 740, 710, 700 cm^{-1}; ^1H NMR δ 7.75−7.68 (m, 4H), 7.44−7.34 (m, 6H), 3.99 (dd, J = 11.2 and 4.6 Hz, 1H), 3.68 (dd, J = 10.4 and 4.5 Hz, 1H), 3.68 (br s, 1H, OH), 3.53 (dd, J = 10.4 and 9.1 Hz, 1H), 3.32 (dd apparent t, J = 11.2 Hz, 1H), 1.39 (m, 1H), 1.22 (m, 1H), 1.07 (s, 9H), 0.98 (d, J = 6.7 Hz, 3H), 0.69 (m, 1H), 0.56 (m, 1H), −0.25 (m, 1H); ^{13}C NMR δ 135.6 (d, 2C), 135.5 (d, 2C), 133.0 (s, 2C), 129.7 (d, 2C), 127.7 (d, 4C), 69.0 (t), 64.6 (t), 35.2 (d), 26.6 (q, 3C), 21.3 (d), 18.9 (s), 18.6 (d), 17.8 (q), 5.7 (t); MS-EI *m*/*z* (relative intensity) 311 (M − *t*-Bu^+, 28), 281 (16), 200 (19), 199 (100). Anal. Calcd for $C_{23}H_{32}O_2Si$: C, 74.95; H, 8.75. Found: C, 75.13; H, 8.73.

(2*R*)-2-{(1*R*,2*R*)-2-[(Benzyloxy)methyl]cyclopropyl}-propanol (6b). This compound was synthesized from **5b** (1.50 g, 7.42 mmol) according to the procedure described for the preparation of **6a** from **5a**. Purification by flash chromatography (petroleum ether/EtOAc gradient 90/10 to 70/30) afforded 1.49 g (91%) of **6b** as a colorless oil: $[\alpha]^{20}_D$ +72.3 (*c* 1.0, $CHCl_3$); IR (film) 3400, 3060, 1090, 1070, 1040, 1030, 750, 740, 700 cm^{-1}; ^1H RMN δ 7.37−7.27 (m, 5H), 4.54 (s, 2H), 3.86 (dd, J = 10.3 and 4.8 Hz, 1H), 3.79 (t, J = 5.1 Hz, 1H, OH), 3.61 (ddd, J = 10.7, 6.3 and 4.4 Hz, 1H), 3.44 (m, 1H), 3.12 (dd apparent t, J = 10.3 Hz, 1H), 1.37−1.21 (m, 2H), 0.97 (d, J = 6.6 Hz, 3H), 0.75−0.62 (m, 2H), −0.11 (m, 1H); ^{13}C NMR δ 154.6 (s), 128.4 (d, 2C), 128.0 (d, 2C), 127.8 (d), 73.0 (t), 70.5 (t), 69.1 (t), 35.2 (d), 21.3 (d), 17.9 (q), 16.3 (d), 6.3 (t); MS-EI *m*/*z* (relative intensity) 220 ($M^{+\bullet}$, 0.02), 107 (12), 92 (16), 91 (100), 81 (11). Anal. Calcd for $C_{14}H_{20}O_2$: C, 76.33; H, 9.15. Found: C, 76.14; H, 9.37.

Ethyl (*E*),(4*R*)-4-((1*R*,2*R*)-2-{[(*tert*-butyldiphenylsilyl)-oxy]methyl}cyclopropyl)pent-2-enoate (8a). To a solution of **6a** (11.6 g, 31.6 mmol) in CH_2Cl_2 (500 mL) at rt, were successively added 4 Å powdered molecular sieves (28 g) and PCC (14.5 g, 67.2 mmol, 2.1 equiv). After 1.5 h at rt, the reaction mixture was diluted with ether and filtered through silica gel (ether). The filtrate was evaporated under reduced pressure and the crude aldehyde **7a**, was directly engaged in the next step without further purification. To a suspension of NaH (1.57 g, 60% dispersion in mineral oil, 39.2 mmol, 1.2 equiv) in THF (200 mL) at 0 °C, was added dropwise triethylphosphonoacetate (8.9 mL, 45 mmol, 1.4 equiv). After 20 min at rt, the reaction mixture was cooled to 0 °C and a solution of **7a** in THF (10 mL) was added dropwise. After 1 h at rt, the reaction mixture was hydrolyzed with a saturated aqueous solution of NH_4Cl and extracted with ether. The combined extracts were washed with brine, dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The crude material was purified by flash chromatography (petroleum ether/Et_2O 93/7) to give 10.7 g (78% from **6a**) of **8a** as a colorless oil: $[\alpha]^{20}_D$ −65.8 (*c* 1.1, $CHCl_3$); IR (film) 3060, 1725, 1715, 1650, 1265, 1245, 1185, 1165, 825, 795, 745, 710, 700, 690 cm^{-1}; ^1H NMR δ 7.73−7.66 (m, 4H), 7.47−7.35 (m, 6H), 7.15 (dd, J = 15.8 and 5.9 Hz, 1H), 5.88 (dd, J = 15.8 and 1.8 Hz, 1H), 4.18 (q, J = 7.1 Hz, 2H), 3.71 (dd, J = 11.0 and 6.3 Hz, 1H), 3.64 (dd, J = 11.0 and 7.7 Hz, 1H), 1.88 (m, 1H), 1.28 (t, J = 7.1 Hz, 3H), 1.21 (m, 1H), 1.16 (d, J = 6.6 Hz, 3H), 1.06 (s, 9H), 0.85−0.65 (m, 2H), −0.01 (m, 1H); ^{13}C NMR δ 167.0 (s), 153.7 (d), 135.6 (d, 2C), 135.5 (d, 2C), 133.9 (s), 133.8 (s), 129.5 (d, 2C), 127.6 (d, 2C), 127.5 (d, 2C), 119.4 (d), 63.7 (t), 60.0 (t), 35.5 (d), 26.8 (q, 3C), 21.8 (d), 19.7 (q), 19.1 (s), 18.7 (d), 14.3 (q), 7.9 (t); MS-EI *m*/*z* (relative intensity) 380 (M − *i*-$C_4H_8^{+\bullet}$, 25), 379 (M − *t*-Bu^+, 83), 227 (50), 199 (100), 197 (23), 183 (59), 181 (26), 139 (15), 135 (47), 107 (28), 105 (18), 91 (16), 79 (23), 77 (15). Anal. Calcd for $C_{27}H_{36}O_3Si$: C, 74.27; H, 8.31. Found: C, 73.89; H, 8.72.

Ethyl (*E*),(4*R*)-4-{(1*R*,2*R*)-2-[(Benzyloxy)methyl]cyclopropyl}pent-2-enoate (8b). To a solution of **6b** (2.72 g, 12.4 mmol) in CH_2Cl_2/MeCN (9/1, 30 mL) at 0 °C were successively added NMO (2.26 g, 19.3 mmol, 1.6 equiv), 4 Å powdered molecular sieves (6.2 g), and TPAP (260 mg, 0.740 mmol, 0.06 equiv). After 45 min at rt, the reaction mixture was concentrated under reduced pressure and the residue was filtered through silca gel (CH_2Cl_2/EtOAc 50/50). The filtrate was evaporated under reduced pressure and the sensitive aldehyde **7b** was directly engaged in the next step without further purification. To a suspension of NaH (788 mg, 60% dispersion in mineral oil, 19.7 mmol, 1.5 equiv) in THF (60 mL) was added dropwise triethyl phosphonoacetate (3.90 mL, 19.7 mmol, 1.5 equiv). The reaction mixture was cooled to 0 °C and a solution of aldehyde **7b** in THF (2 mL) was added dropwise. After 50 min at rt, the reaction mixture was hydrolyzed with a saturated aqueous solution of NH_4Cl and extracted with ether (3 × 20 mL) and EtOAc (2 × 30 mL). The combined extracts were washed with brine, dried over $MgSO_4$, filtered and concentrated under reduced pressure. The crude material was purified by flash chromatography (petroleum ether/EtOAc 90/10) to afford 2.00 g (56% from **6b**) of **8b** as a colorless oil: $[\alpha]^{20}_D$ −113.7 (*c* 1.1, $CHCl_3$); IR (film) 1725, 1715, 1650, 1285, 1270, 1185, 1090, 1075, 1030, 745, 700 cm^{-1}; ^1H NMR δ 7.36−7.24 (m, 5H), 7.10 (dd, J = 15.8 and 6.3 Hz, 1H), 5.86 (dd, J = 15.8 and 1.5 Hz, 1H), 4.51 (s, 2H), 4.19 (q, J = 7.2 Hz, 2H), 3.53 (dd, J = 10.1 and 7.2 Hz, 1H), 3.44 (dd, J = 10.1 and 7.2 Hz, 1H), 1.86 (m, 1H), 1.29 (t, J = 7.2 Hz, 3H), 1.28 (m, 1H), 1.18 (d, J = 6.6 Hz, 3H), 0.87−0.75 (m, 2H), 0.12 (m, 1H); ^{13}C NMR δ 166.9 (s), 153.5 (d), 138.4 (s), 128.3 (d, 2C), 127.7 (d, 2C), 127.5 (d), 119.3 (d), 72.7 (t), 70.1 (t), 60.1 (t), 36.0 (d), 21.5 (d), 19.7 (q), 16.1 (d), 14.2 (q), 8.8 (t); MS-EI *m*/*z* (relative intensity) 243 (M − OEt^+, 0.2), 197 (M − Bn^+, 3), 188 (4), 141 (10), 108 (10), 107 (14), 92 (11), 91 (100), 79 (10). Anal. Calcd for $C_{18}H_{24}O_3$: C, 74.97; H, 8.39. Found: C, 74.92; H, 8.56.

Ethyl (4*S*)-4-((1*R*,2*R*)-2-{[(*tert*-Butyldiphenylsilyl)oxy]-methyl}cyclopropyl)pentanoate (9a). To a solution of **8a** (2.20 g, 5.04 mmol) in EtOAc (30 mL) was added PtO_2 (70 mg, 0.31 mmol, 0.06 equiv), and the resulting mixture was stirred under an atmosphere of hydrogen. After 6 h, the reaction mixture was filtered through Celite, and the filtrate was evaporated under reduced pressure. The residue was purified by flash chromatography (petroleum ether/EtOAc 93/7) to give 2.15 g (97%) of **9a** as a colorless oil: $[\alpha]^{20}_D$ −16.6 (*c* 1.1, $CHCl_3$); IR (film) 3060, 1735, 1590, 1260, 1175, 1105, 1065, 820, 790, 745, 710, 700, 690 cm^{-1}; ^1H NMR δ 7.75−7.69 (m, 4H), 7.48−7.37 (m, 6H), 4.10 (q, J = 7.0 Hz, 2H), 3.74 (dd, J = 11.1 and 6.3 Hz, 1H), 3.64 (dd, J = 11.1 and 7.9 Hz, 1H), 2.43−2.27 (m, 2H), 1.98 (m, 1H), 1.66 (m, 1H), 1.23 (t, J = 7.2 Hz, 3H), 1.20−0.98 (m, 5H), 1.08 (s, 9H), 0.73−0.57 (m, 2H), −0.14 (m, 1H); ^{13}C NMR δ 174.0 (s), 135.6 (d, 2C), 135.5 (d, 2C), 134.0 (s, 2C), 129.5 (d, 2C), 127.6 (d, 2C), 127.5 (d, 2C), 64.1 (t), 60.0 (t), 32.3 (t), 32.2 (t+d,2C), 26.8 (q, 3C), 23.7 (d), 19.9 (q), 19.1 (s), 18.9 (d), 14.2 (q), 7.8 (t); MS-EI *m*/*z* (relative intensity) 382 (M − *i*-$C_4H_8^{+\bullet}$, 27), 381 (M − *t*-Bu^+, 88), 227 (20), 199 (100), 197 (23), 183 (34), 181 (22), 139 (36), 135 (27), 95 (15), 77 (11), 55 (10). Anal. Calcd for $C_{27}H_{38}O_3Si$: C, 73.93; H, 8.73. Found: C, 73.51; H, 9.03.

Ethyl (4*S*)-4-{(1*R*,2*R*)-2-[(Benzyloxy)methyl]cyclopropyl}pentanoate (9b). This compound was synthesized from **8b** (1.55 g, 5.38 mmol) according to the procedure described for the preparation of **9a** from **8a**. Purification by flash chromatography (petroleum ether/EtOAc 90/10) afforded 1.49 g (95%) of **9b** as a colorless oil: $[\alpha]^{20}_D$ −17.2 (*c* 1.0, $CHCl_3$); IR (film) 1730, 1260, 1180, 1090, 1030, 750, 740, 700 cm^{-1}; ^1H NMR δ 7.35−7.24 (m, 5H), 4.55 (d, J = 12.0 Hz, 1H), 4.50 (d, J = 12.0 Hz, 1H), 4.10 (q, J = 7.2 Hz, 2H), 3.51 (dd, J = 10.1 and 7.5 Hz, 1H), 3.43 (dd, J = 10.1 and 7.2 Hz, 1H), 2.41−2.22 (m, 2H), 1.88 (m, 1H), 1.57 (m, 1H), 1.24 (t, J = 7.2 Hz, 3H), 1.21 (m, 1H), 1.00 (br s, 3H), 1.05−0.95 (m, 1H), 0.77−0.63 (m, 2H), −0.03 (m, 1H); ^{13}C NMR δ 174.0 (s), 138.6 (s), 128.3 (d, 2C), 127.7 (d, 2C), 127.5 (d), 72.8 (t), 70.5 (t), 60.1 (t), 32.5 (d), 32.2 (t), 32.1 (t), 23.4 (d), 19.9 (q), 16.3 (d), 14.2 (q), 8.5 (t); MS-EI *m*/*z* (relative intensity) 290 ($M^{+\bullet}$, 0.1), 199 (2), 183 (4), 153 (4), 142 (8), 108 (10), 95 (10), 92 (13), 91 (100). Anal. Calcd for $C_{18}H_{26}O_3$: C, 74.45; H, 9.02. Found: C, 74.59; H, 9.24.

(4*S*)-4-((1*R*,2*R*)-2-{[(*tert*-Butyldiphenylsilyl)oxy]methyl}-cyclopropyl)pentanal (10a). To a solution of **9a** (2.73 g, 6.22 mmol) in toluene (30 mL) at −78 °C was added dropwise Dibal-H (6.4 mL, 1 M in hexanes, 6.4 mmol, 1.03 equiv). After 1 h at −78 °C, the reaction mixture was poured into a saturated aqueous solution of Rochelle's salt (15 mL) and ether (20 mL) was added. After the mixture was stirred for 3 h at rt, the layers were separated, the aqueous phase was extracted with ether, and the combined extracts were washed with brine, dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The crude material was purified by flash chromatography (petroleum ether/EtOAc gradient 100/0 at 95/5) to give 2.39 g (97%) of **10a** as a colorless oil: $[\alpha]^{20}_D$ −13.3 (*c* 1.0, $CHCl_3$); IR (film) 3060, 2710, 1725, 1715, 1110, 1060, 825, 790, 745, 710, 700 cm^{-1}; ^1H NMR δ 9.71 (t, J = 1.8 Hz, 1H), 7.71−7.65 (m, 4H), 7.44−7.35 (m, 6H), 3.78 (dd, J = 11.1 and 5.7 Hz, 1H), 3.53 (dd, J = 11.1 and 8.5 Hz, 1H), 2.53−2.34 (m, 2H), 1.99 (m, 1H), 1.63 (m, 1H), 1.21−1.00 (m, 2H), 1.05 (s, 9H), 0.97 (d, J = 6.2 Hz, 3H), 0.70−0.55 (m, 2H), −0.17 (m, 1H); ^{13}C NMR δ 203.0 (d), 135.6 (d, 2C), 135.5 (d, 2C), 133.9 (2s, 2C), 129.6 (d, 2C), 127.6 (d+d, 2C+2C), 64.1 (t), 41.7 (t), 32.1 (d), 29.4 (t), 26.9 (q, 3C), 23.7 (d), 20.0 (q), 19.2 (s), 18.9 (d), 7.6 (t); MS-EI *m*/*z* (relative intensity) 337 (M − *t*-Bu^+, 10), 281 (14), 259 (9), 203 (20), 200 (18), 199 (100), 181 (16), 183 (20), 139 (11), 135 (10), 121 (26). Anal. Calcd for $C_{25}H_{34}O_2Si$: C, 76.09; H, 8.68. Found: C, 76.13; H, 8.82.

(4*S*)-4-{(1*R*,2*R*)-2-[(Benzyloxy)methyl]cyclopropyl}-pentanal (10b). This compound was synthesized from **9b** (1.29 g, 4.43 mmol) according to the procedure described for the preparation of **10a** from **9a**. Purification by flash chromatography (petroleum ether/EtOAc 90/10) afforded 978 mg (90%) of **10b** as a colorless oil: $[\alpha]^{20}_D$ 0.0 (*c* 1.2, $CHCl_3$); IR (film) 3060, 3020, 2720, 1720, 1090, 1075, 1025, 750, 740, 700 cm^{-1}; ^1H NMR δ 9.69 (t, J = 1.8 Hz, 1H), 7.36−7.26 (m, 5H), 4.55 (d, J = 11.8 Hz, 1H), 4.49 (d, J = 11.8 Hz, 1H), 3.55 (dd, J = 10.1 and 6.5 Hz, 1H), 3.39 (dd, J = 10.1 and 8.3 Hz, 1H), 2.52−2.33 (m, 2H), 1.93 (m, 1H), 1.59 (m, 1H), 1.22 (m, 1H), 1.01 (m, 1H), 1.01 (s, 3H), 0.77−0.61 (m, 2H), −0.04 (m, 1H); ^{13}C NMR δ 203.0 (d), 138.4 (s), 128.3 (d, 2C), 127.7 (d, 2C), 127.5 (d), 72.8 (t), 70.5 (t), 41.5 (t), 32.2 (d), 29.3 (t), 23.5 (d), 20.0 (q), 16.3 (d), 8.2 (t); MS-EI *m*/*z* (relative intensity) 246 ($M^{+\bullet}$, 0.1), 140 (3), 122 (4), 107 (12), 94 (11), 92 (18), 91 (100), 79 (11). Anal. Calcd for $C_{16}H_{22}O_2$: C, 78.01; H, 9.00. Found: C, 77.80; H, 8.99.

(1*S*,3*S*,4*S*,7*S*)-7-((1*R*,2*R*)-2-{[(*tert*-Butyldimethylsilyl)-oxy]methyl}cyclopropyl)-4-hydroxy-1,3-dimethyl-2-oxo-octylbenzoate (12a). To a solution of (*c*-Hex)$_2$BCl (1.3 mL, 6.2 mmol, 2.8 equiv) in Et_2O (6 mL) at −78 °C were successively added dropwise $EtNMe_2$ (0.80 mL, 7.41 mmol, 3.4 equiv) and a solution of ethyl ketone (*R*)-**11**[31] (850 mg, 4.14 mmol, 1.9 equiv) in Et_2O (16 mL). After 2 h at 0 °C, the reaction mixture was cooled to −78 °C and a solution of aldehyde **10a** (860 mg, 2.18 mmol) in Et_2O (3 mL) was added dropwise. After 4 h at −78 °C and 16 h at −23 °C, the reaction mixture was warmed to 0 °C and a MeOH/phosphate buffer (pH 7) mixture (1/1, 32 mL) and a 30% aqueous solution of H_2O_2 (16 mL) were successively added dropwise. After 1 h at 0 °C, the resulting mixture was extracted with CH_2Cl_2, and the combined extracts were dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The crude material was purified by flash chromatography (petroleum ether/EtOAc gradient 94/6 to 90/10) to afford 1.09 g (83%) of **12a** as a colorless oil: $[\alpha]^{20}_D$ −23.5 (*c* 1.0, $CHCl_3$); IR (film) 3520, 3070, 1725, 1715, 1270, 1070, 1030, 1000, 1110, 825, 745, 710, 700, 690 cm^{-1}; ^1H NMR δ 8.08 (m, 2H), 7.72−7.65 (m, 4H), 7.57 (m, 1H), 7.47−7.33 (m, 8H), 5.39 (q, J = 7.0 Hz, 1H), 3.73 (dd, J = 11.2 and 6.1 Hz, 1H), 3.71 (m, 1H), 3.59 (dd, J = 11.2 and 8.3 Hz, 1H), 2.81 (qd, apparent quintet, J = 7.3 Hz, 1H), 2.53 (d, J = 5.5 Hz, 1H, OH), 1.76 (m, 1H), 1.54−1.34 (m, 3H), 1.52 (d, J = 7.0 Hz, 3H), 1.18 (d, J = 7.4 Hz, 3H), 1.13−0.95 (m, 2H), 1.05 (s, 9H), 0.97 (br s, 3H), 0.67 (m, 1H), 0.56 (m, 1H), −0.18 (m, 1H); ^{13}C NMR δ 211.5 (s), 165.8 (s), 135.6 (d, 2C), 135.5 (d, 2C), 133.9 (s, 2C), 133.2 (d), 129.7 (d, 2C), 129.5 (2d + s, 2C + 1C), 128.4 (d, 2C), 127.6 (d, 2C), 127.5 (d, 2C), 74.7 (d), 73.2 (d), 64.4 (t), 48.5 (d), 32.8 (t), 32.1 (d), 31.8 (t), 26.9 (q, 3C), 24.2 (d), 19.8 (q), 19.1 (s), 18.6 (d), 15.6 (q), 14.3 (q), 7.9 (t).

(1*S*,3*S*,4*S*,7*S*)-7-{(1*R*,2*R*)-2-[(Benzyloxy)methyl]cyclopropyl}-4-hydroxy-1,3-dimethyl-2-oxooctylbenzoate (12b). This compound was synthesized from **10b** (89 mg, 0.36 mmol) and ethyl ketone (*R*)-**11**[31] (159 mg, 0.771 mmol, 2.1 equiv) according to the procedure described for the preparation of **12a** from **10a** and (*R*)-**11**. Two successive purifications by flash chromatography (CH_2Cl_2/Et_2O gradient 99/1 to 94/6) afforded 142 mg (87%) of **12b** as a colorless solid: mp 66 °C; $[\alpha]^{20}_D$ −23.7 (*c* 0.5, $CHCl_3$); IR ($CHBr_3$) 3480, 1720, 1270, 1070, 1030, 1000, 715 cm^{-1}; ^1H NMR δ 8.09 (m, 2H), 7.59 (m, 1H), 7.49−7.43 (m, 2H), 7.35−7.24 (m, 5H), 5.40 (q, J = 7.0 Hz, 1H), 4.55 (d, J = 11.8 Hz, 1H), 4.50 (d, J = 11.8 Hz, 1H), 3.73 (m, 1H), 3.56 (dd, J = 10.7 and 6.6 Hz, 1H), 3.40 (dd, J = 10.7 and 8.8 Hz, 1H), 2.82 (dq, apparent quintet, J = 7.3 Hz, 1H), 2.73 (d, J = 5.5 Hz, 1H, OH), 1.70 (m, 1H), 1.54 (d, J = 7.0 Hz, 3H), 1.56−1.32 (m, 3H), 1.25−1.12 (m, 1H), 1.19 (d, J = 7.0 Hz, 3H), 1.04−0.93 (m, 1H), 0.99 (br s, 3H), 0.74−0.67 (m, 2H), −0.05 (m, 1H); ^{13}C NMR δ 211.5 (s), 165.8 (s), 138.4 (s), 133.2 (d), 129.8 (d, 2C), 129.6 (s), 128.4 (d, 2C), 128.3 (d, 2C), 127.7 (d, 2C), 127.5 (d), 74.8 (d), 72.8 (d), 72.6 (t), 70.8 (t), 48.5 (d), 32.6 (t), 31.8 (d), 31.5 (t), 24.1 (d), 19.9 (q), 16.0 (d), 15.6 (q), 14.2 (q), 8.5 (t). Anal. Calcd for $C_{28}H_{36}O_5$: C, 74.31; H, 8.02. Found: C, 74.15; H, 8.22.

(1*S*,3*S*,4*S*,7*S*)-4-Hydroxy-7-[(1*R*,2*R*)-2-(hydroxymethyl-)cyclopropyl]-1,3-dimethyl-2-oxooctylbenzoate (12c). To a solution of **12a** (0.18 g, 0.30 mmol) in THF (7 mL) [polyethylene container] at 0 °C was added dropwise HF·Pyridine (0.7 mL). After 2 h at rt, the reaction mixture was diluted with water and ether and neutralized by portionwise addition of solid $NaHCO_3$. The resulting mixture was extracted with ether, and the combined extracts were dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The crude material was crystallized from pentane/CH_2Cl_2 to afford 93 mg (86%) of **12c** as a white solid: mp 123 °C; $[\alpha]^{20}_D$ −29.8 (*c* 1.0, $CHCl_3$); IR (KBr) 3420, 3289, 1733, 1719, 1290, 1268, 1122, 1000, 713 cm^{-1}; ^1H NMR δ 8.08 (m, 2H), 7.59 (m, 1H), 7.46 (m, 2H), 5.44 (q, J = 7.1 Hz, 1H), 3.82 (dd, J = 11.6 and 5.9 Hz, 1H), 3.78 (m, 1H), 3.40 (dd, J = 11.6 and 9.4 Hz, 1H), 3.19 (br s, 1H, OH), 2.87 (dq, apparent quintet, J = 7.3 Hz, 1H), 2.24 (br s, 1H, OH), 1.80 (m, 1H), 1.57 (m, 1H), 1.57 (d, J = 7.0 Hz, 3H), 1.48−1.32 (m, 2H), 1.24 (d, J = 7.0 Hz, 3H), 1.18−1.02 (m, 2H), 0.99 (d, J = 5.9 Hz, 3H), 0.75−0.62 (m, 2H), −0.01 (m, 1H); ^{13}C NMR δ 211.8 (s), 165.9 (s), 133.3 (d), 129.8 (d, 2C), 129.5 (s), 128.4 (d, 2C), 74.8 (d), 72.3 (d), 63.3 (t), 48.4 (d), 32.6 (t), 31.0 (t), 30.9 (d), 24.4 (d), 19.8 (q), 18.7 (d), 15.8 (q), 14.3 (q), 8.0 (t); MS-CI^+ (CH_4) *m*/*z* (relative intensity) 345 ($M + H^+ - H_2O$, 52), 223 (23), 207 (98), 205 (19), 139 (100), 121 (50), 105 (87); HRMS (CI^+, CH_4) calcd for $C_{21}H_{31}O_5$ ($M + H^+$) 363.2171, found 363.2169.

(1*R*,3*S*)-3-[(2*S*,5*S*,6*S*)-6-((1*S*)-2-Benzyloxy-1-methylethyl)-5-methyltetrahydro-2*H*-pyran-2-yl]-1-methyl-2-oxobutyl-benzoate (14b). To a degassed solution of **12b** (137 mg, 0.303 mmol) in CH_2Cl_2 (14 mL) (argon bubbling, 15 min) was added mercuric trifluoroacetate (292 mg, 0.684 mmol, 2.3 equiv). After 30 min at rt with exclusion of light, the reaction mixture was hydrolyzed with a saturated aqueous solution of KBr (4 mL). After 20 min, the resulting mixture was extracted with EtOAc. The combined extracts were dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The crude mixture of organomercuric bromides was dissolved in THF/toluene (1/1, 8 mL), and to the resulting degassed solution [argon bubbling, 30 min] were added a catalytic amount of AIBN (ca. 4 mg) and *n*-Bu_3SnH (0.30 mL, 1.1 mmol, 3.7 equiv). After 1 h at rt and 1 h at 55 °C, CCl_4 (1 mL) was added. After 1 h at rt, the reaction mixture was diluted with petroleum ether/CH_2Cl_2 (75/25, 20 mL), metallic mercury was removed by filtration through glass wool and the filtrate was washed with a 5% aqueous solution of KF (4 × 10 mL). The organic layer was

dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was taken up in CH_2Cl_2 and the resulting mixture was filtered through glass wool. Analysis of the ^1H NMR spectrum of the crude material indicated the formation of two diastereomers **14b** and **14′b** (**14b**/**14′b** = 85/15). After purification by flash chromatography (petroleum ether/EtOAc gradient 95/15 to 90/10), 63 mg (46%) of a diastereomeric mixture of **14b** et **14′b** (85/15 ratio) was obtained as a colorless oil. An analytical sample of the separated major diastereomer was used for characterization (only the signals corresponding to the major diatereomer **14b** could be fully attributed with certainty): $[\alpha]^{20}_D$ +18.1 (*c* 1.40, $CHCl_3$); IR (film) 1725, 1715, 1265, 1115, 715 cm^{-1}; ^1H NMR δ 8.09 (m, 2H), 7.58 (m, 1H), 7.46 (m, 2H), 7.37−7.24 (m, 5H), 5.45 (q, J = 7.0 Hz, 1H), 4.50 (d, J = 12.1 Hz, 1H), 4.42 (d, J = 12.1 Hz, 1H), 3.82 (ddd, apparent td, J = 9.0 and 4.2 Hz 1H), 3.35 (dd, J = 9.2 and 5.2 Hz, 1H), 3.25 (dd, J = 9.2 and 5.9 Hz, 1H), 3.20 (dd, J = 8.1 and 4.4 Hz, 1H), 3.06 (dq, J = 9.6 and 7.0 Hz, 1H), 2.17 (m, 1H), 1.77−1.68 (m, 2H), 1.59−1.45 (m, 2H), 1.51 (d, J = 7.0 Hz, 3H), 1.31 (m, 1H), 1.07 (d, J = 7.0 Hz, 3H), 0.94 (d, J = 7.0 Hz, 3H), 0.88 (d, J = 6.6 Hz, 3H); ^{13}C NMR δ 210.4 (s), 165.7 (s), 138.7 (s), 133.1 (d), 129.8 (d, 2C), 129.8 (s), 128.4 (d, 2C), 128.3 (d, 2C), 127.4 (d, 2C), 127.3 (d), 79.5 (d), 75.4 (d), 73.7 (t), 72.9 (t), 72.4 (d), 46.5 (d), 33.4 (d), 28.3 (d), 25.4 (t), 24.2 (t), 18.2 (q), 15.4 (q), 13.5 (q), 13.0 (q); MS-CI$^+$(CH_4) *m*/*z* (relative intensity) 453 (M + H$^+$, 36), 333 (32), 303 (30), 255 (42), 247 (100), 155 (57), 139 (30), 123 (20); HRMS (CI$^+$, CH_4) calcd for $C_{28}H_{37}O_5$ (M + H$^+$) 453.2641, found 453.2646.

(1*R*,3*R*)-3-[(2*S*,5*S*,6*S*)-6-((1*S*)-2-Hydroxymethyl-1-methylethyl)-5-methyltetrahydro-2*H*-pyran-2-yl]-1-methyl-2-oxobutylbenzoate (14′c) and (1*R*,3*R*)-3-[(2*S*,5*S*,6*R*)-6-((1*S*)-2-Hydroxymethyl-1-methylethyl)-5-methyltetrahydro-2*H*-pyran-2-yl]-1-methyl-2-oxobutylbenzoate (14′c). Following the procedure described for the preparation of **14b/14′b** from **12b**, compound **12c** (206 mg, 0.569 mmol) underwent an intramolecular oxymercuration with mercuric trifluoroacetate (532 mg, 1.25 mmol, 2.2 equiv) and a subsequent reductive demercuration with *n*-Bu_3SnH (0.38 mL, 1.4 mmol, 2.5 equiv) in the presence of a catalytic amount of AIBN (ca. 4 mg). Analysis of the ^1H NMR spectrum of the crude material indicated the formation of two diastereomers **14c** and **14′c** (**14c**/**14′c** = 93/7). Purification by flash chromatography (petroleum ether/EtOAc 80/20) afforded 176 mg (85%) of a diastereomeric mixture of **14c** and **14′c** (93/7 ratio) as a colorless oil: $[\alpha]^{20}_D$ +44.0 (*c* 0.04, $CHCl_3$); IR (film) 3440, 1720, 1270, 1120, 720 cm^{-1}; ^1H NMR (only the signals corresponding to the major diastereomer **14c** could be fully attributed with certainty) δ 8.08 (m, 2H), 7.59 (m, 1H), 7.48 (m, 2H), 5.60 (q, J = 6.9 Hz, 1H), 4.09 (m, 1H), 3.52 (m, 2H), 3.36−3.24 (m, 2H), 2.28 (br s, 1H, OH), 1.89 (m, 1H), 1.67−1.60 (m, 3H), 1.55 (d, J = 6.8 Hz, 3H), 1.30−1.21 (m, 2H), 1.08 (d, J = 7.0 Hz, 3H), 0.87 (d, J = 7.0 Hz, 3H), 0.84 (d, J = 6.5 Hz, 3H); ^{13}C NMR (only the signals corresponding to the major diastereomer **14c** could be fully attributed with certainty) δ 210.3 (s), 165.8 (s), 133.3 (d), 129.8 (d, 2C), 129.6 (s), 128.5 (d, 2C), 78.8 (d), 74.7 (d), 73.2 (d), 66.6 (t), 43.9 (d), 35.6 (d), 30.3 (d), 26.4 (t), 24.8 (t), 17.9 (q), 16.1 (q), 13.9 (q), 10.4 (q); MS-CI$^+$ (CH_4) *m*/*z* (relative intensity) 363 (M + H$^+$, 100), 241 (20), 207 (22), 157 (92), 139 (61); HRMS (CI$^+$, CH_4) calcd for $C_{21}H_{31}O_5$ (M + H$^+$) 363.2171, found 363.2169.

(1*R*,3*S*)-3-((2*S*,5*S*,6*S*)-6-{(1*S*)-2-[(*tert*-Butyldiphenylsilyl)oxy]-1-methylethyl}-5-methyltetrahydro-2*H*-pyran-2-yl)-1-methyl-2-oxobutylbenzoate (14a) and (1*R*,3*S*)-3-((2*S*,5*S*,6*S*)-6-{(1*R*)-2-[(*tert*-Butyldiphenylsilyl)oxy]-1-methylethyl}-5-methyltetrahydro-2*H*-pyran-2-yl)-1-methyl-2-oxobutylbenzoate (14′a). To a solution of **14c** and **14′c** (93/7 ratio, 987 mg, 2.72 mmol) in DMF (3 mL) were added imidazole (413 mg, 6.07 mmol, 2.2 equiv) and *tert*-butylchlorodiphenylsilane. After 5 h at rt, the reaction mixture was hydrolyzed with a saturated aqueous solution of NH_4Cl and extracted with petroleum ether/CH_2Cl_2 (9/1). The combined extracts were washed with brine, dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The crude material was purified by flash chromatography (petroleum ether/EtOAc gradient 95/5 to 90/10) to afford 1.52 g (93%) of **14a** and 98 mg (6%) of **14′a** as colorless oils.

Major diastereomer **14a**: R_f 0.41 (petroleum ether/EtOAc 80/20); $[\alpha]^{20}_D$ −2.86 (*c* 0.07, $CHCl_3$); IR (film) 3070, 1720, 1270, 1110, 825, 750, 710, 705 cm^{-1}; ^1H NMR δ 8.08 (m, 2H), 7.73−7.55 (m, 5H), 7.46−7.34 (m, 8H), 5.39 (q, J = 6.9 Hz, 1H), 3.69 (ddd, apparent td, J = 9.2 and 3.9 Hz, 1H), 3.52 (dd, J = 10.2 and 4.4 Hz, 1H), 3.46 (dd, J = 10.2 and 5.3 Hz, 1H), 3.19 (dd, J = 9.2 and 2.2 Hz, 1H), 2.96 (dq, J = 9.2 and 7.0 Hz, 1H), 2.06 (m, 1H), 1.78−1.59 (m, 3H), 1.48 (d, J = 7.0 Hz, 3H), 1.40−1.27 (m, 2H), 1.06 (d, J = 7.4 Hz, 3H), 1.04 (s, 9H), 0.94 (d, J = 7.0 Hz, 3H), 0.87 (d, J = 6.6 Hz, 3H); ^{13}C NMR δ 210.8 (s), 165.7 (s), 135.6 (d, 2C), 134.8 (d), 133.8 (s, 2C), 133.1 (d), 129.9 (s), 129.8 (d, 2C), 129.5 (d, 2C), 128.3 (d, 2C), 127.7 (d), 127.6 (d, 4C), 80.0 (d), 75.5 (d), 72.1 (d), 66.9 (t), 47.4 (d), 35.1 (d), 27.6 (d), 26.8 (q, 3C), 24.9 (t), 23.8 (t), 19.3 (s), 18.3 (q), 15.2 (q), 13.4 (q), 13.2 (q); MS-EI *m*/*z* (relative intensity) 543 (M − *t*-Bu$^+$, 5), 309 (15), 303 (100), 183 (12), 135 (14), 105 (61); HRMS (CI$^+$, CH_4) calcd for $C_{37}H_{49}O_5Si$ (M + H$^+$) 601.3349, found 601.3347.

Minor diastereomer **14′a**: R_f 0.50 (petroleum ether/EtOAc 80/20); $[\alpha]^{20}_D$ +16.9 (*c* 0.75, $CHCl_3$); IR (film) 1720, 1270, 1110, 1005, 825, 745, 715, 705, 690 cm^{-1}; ^1H NMR δ 8.05 (m, 2H), 7.66−7.63 (m, 4H), 7.57 (m, 1H), 7.46−7.33 (m, 8H), 5.35 (q, J = 7.0 Hz, 1H), 3.68 (dd, J = 9.6 and 8.1 Hz, 1H), 3.49 (dd, J = 9.6 and 6.4 Hz, 1H), 3.40 (m, 1H), 3.20 (dd, J = 9.7 and 1.7 Hz, 1H), 2.95 (qd, apparent quintet, J = 7.0 Hz, 1H), 1.93 (m, 1H), 1.76 (m, 1H), 1.56 (m, 1H), 1.46 (m, 1H), 1.45 (d, J = 7.0 Hz, 3H), 1.26−1.15 (m, 2H), 1.14 (d, J = 7.0 Hz, 3H), 1.05 (s, 9H), 0.76 (d, J = 7.0 Hz, 3H), 0.76 (d, J = 6.6 Hz, 3H); ^{13}C NMR δ 209.5 (s), 165.8 (s), 135.6 (d, 4C), 134.2 (s, 2C), 133.2 (d), 129.8 (d, 2C), 129.6 (s), 129.5 (d, 2C), 128.4 (d, 2C), 127.5 (d, 4C), 82.5 (d), 78.5 (d), 74.7 (d), 66.4 (t), 48.0 (d), 36.9 (d), 33.0 (t), 31.4 (d), 28.9 (t), 26.9 (q, 3C), 19.3 (s), 17.2 (q), 15.6 (q), 13.6 (q), 9.5 (q); MS-EI *m*/*z* (relative intensity) 543 (M − *t*-Bu$^+$, 12), 309 (17), 304 (26), 303 (100), 243 (16), 199 (32), 183 (16), 135 (15), 121 (12) 105 (76), 77 (10).

(2*S*)-2-((2*S*,5*S*,6*S*)-6-{(1*S*)-2-[(*tert*-Butyldiphenylsilyl)-oxy]-1-methylethyl}-5-methyltetrahydro-2*H*-pyran-2-yl)-propanoic Acid (17). To a solution of **14a** (250 mg, 0.416 mmol) in THF (10 mL) at −78 °C was added a solution of $LiBH_4$ (530 mg, 24.3 mmol, 58 equiv) in THF (10 mL). The reaction mixture was warmed to rt, and 15 h later, an additional quantity of $LiBH_4$ (297 mg, 13.6 mmol, 32 equiv) was added. After 24 h, the reaction mixture was cautiously hydrolyzed with water and extracted with ether. The combined extracts were dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The resulting crude 1,2-diol **15** was dissolved in MeOH/H_2O (2/1, 9 mL), and $NaIO_4$ (755 mg, 3.53 mmol, 8.5 equiv) was added. After 2 h at rt, the reaction mixture was diluted with water and extracted with ether. The combined extracts were dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The resulting crude aldehyde **16** was dissolved in *t*-BuOH (7 mL) and H_2O (2 mL), and 2-methyl-2-butene (0.50 mL, 4.7 mmol, 10 equiv), NaH_2PO_4 monohydrate (635 mg, 4.60 mmol, 11 equiv), and $NaClO_2$ (235 mg, 2.60 mmol, 6 equiv) were added successively at rt. After 1.5 h, the reaction mixture was hydrolyzed with a 1 M aqueous solution of HCl (10 mL) and extracted with ether. The combined extracts were dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The crude material was purified by flash chromatography (petroleum ether/EtOAc: 80/20) to afford 176 mg (90%, 3 etapes) of **17** as a colorless oil: $[\alpha]^{20}_D$ +19.7 (*c* 0.9, $CHCl_3$); IR (film) 3600−2300 (br), 1705, 1105, 1015, 820, 740, 705 cm^{-1}; ^1H NMR δ 7.67−7.62 (m, 4H), 7.46−7.34 (m, 6H), 3.74 (m, 1H), 3.59 (dd, J = 10.3 and 5.5 Hz, 1H), 3.54−3.47 (m, 2H), 2.69 (dq, apparent quintet, J = 7.3 Hz, 1H), 2.03 (m, 1H), 1.80−1.50 (m, 4H), 1.29 (m, 1H), 1.15 (d, J = 7.0 Hz, 3H), 1.05 (s, 9H), 0.97 (d, J = 7.0 Hz, 3H),

0.95 (d, J = 6.6 Hz, 3H); ^{13}C NMR δ 177.2 (s), 135.6 (d, 4C), 133.8 (s), 133.7 (s), 129.5 (d, 2C), 127.6 (d, 4C), 79.2 (d), 72.7 (d), 66.7 (t), 42.5 (d), 35.4 (d), 28.8 (d), 26.9 (q, 3C), 25.4 (t), 24.2 (t), 19.2 (s), 18.1 (q), 13.7 (q), 12.1 (q); MS-CI$^+$ (CH_4) m/z (relative intensity) 469 (M + H$^+$, 78), 347 (59), 333 (85), 313 (80), 289 (54), 269 (100), 213 (65), 195 (37), 139 (38); HRMS (CI$^+$, CH_4) calcd for $C_{28}H_{41}O_4Si$ (M + H$^+$) 469.2774, found 469.2779.

Methyl (2*S*)-2-((2*S*,5*S*,6*S*)-6-{(1*S*)-2-[(*tert*-Butyldiphenylsilyl)oxy]-1-methylethyl}-5-methyl-tetrahydro-2*H*-pyran-2-yl)propanoate (18). To a solution of **17** (159 mg, 0.339 mmol) in C_6H_6 (10 mL) and CH_3OH (4 mL) was added trimethylsilyldiazomethane (0.60 mL, 2 M in hexanes, 1.2 mmol, 3.5 equiv) so that a bright yellow color persisted. After 1.5 h at rt, the reaction mixture was concentrated under reduced pressure and the crude material was purified by flash chromatography (petroleum ether/Et_2O 90/10) to afford 139 mg (85%) of **18** as a colorless oil: $[\alpha]^{20}_D$ +36.1 (*c* 1.0, $CHCl_3$); IR (film) 1740, 1265, 1195, 1165, 1110, 1065, 1015, 820, 740, 705, 690 cm^{-1}; ^{1}H NMR δ 7.72−7.67 (m, 4H), 7.47−7.36 (m, 6H), 3.78 (m, 1H), 3.59 (dd, J = 9.9 and 4.4 Hz, 1H), 3.50 (dd, J = 9.9 and 7.7 Hz, 1H), 3.35 (s, 3H), 3.32 (m, 1H), 2.82 (dq, J = 9.9 and 7.0 Hz, 1H), 2.02 (m, 1H), 1.72−1.51 (m, 4H), 1.28 (m, 1H), 1.08 (s, 9H), 1.04 (d, J = 7.0 Hz, 3H), 1.00 (d, J = 6.6 Hz, 3H), 0.93 (d, J = 6.6 Hz, 3H); ^{13}C NMR δ 175.7 (s), 135.6 (d, 4C), 134.1 (s), 133.9 (s), 129.5 (d, 2C), 127.5 (d, 4C), 78.1 (d), 73.5 (d), 67.5 (t), 51.2 (q), 41.8 (d), 36.2 (d), 29.9 (d), 26.8 (q, 3C), 26.2 (t), 24.2 (t), 19.2 (s), 18.0 (q), 14.0 (q), 11.1 (q); MS-EI m/z (relative intensity) 467 (M − Me$^+$, 0.1), 426 (M − i-$C_4H_8^{+\bullet}$, 28), 451 (M − OMe$^+$, 2), 425 (M − t-Bu$^+$, 85), 396 (20), 395 (63), 214 (20), 213 (100), 199 (93), 197 (22), 183 (55), 181 (21), 177 (27), 153 (24), 149 (23), 135 (31), 121 (52). Anal. Calcd for $C_{29}H_{42}O_4Si$: C, 72.16; H, 8.77. Found: C, 72.16; H, 8.90.

Methyl (2*S*)-2-[(2*S*,5*S*,6*S*)-6-((1*S*)-2-Hydroxy-1-methylethyl)-5-methyltetrahydro-2*H*-pyran-2-yl]propanoate (19). To a solution of **18** (839 mg, 1.74 mmol) in THF (20 mL) (polyethylene container) at 0 °C was added HF·Pyridine (4.0 mL). After 8 h at rt, the reaction mixture was diluted with water and ether and cautiously neutralized by portionwise addition of solid $NaHCO_3$. The resulting mixture was extracted with ether, and the combined extracts were dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The residual traces of pyridine were removed from the crude material by evaporation with cyclohexane under reduced pressure and the residue was purified by flash chromatography (petroleum ether/EtOAc gradient 80/20 to 60/40) to afford 383 mg (90%) of **19** as a colorless oil: $[\alpha]^{20}_D$ +65.6 (*c* 1.2, $CHCl_3$); IR (film) 3460, 1740, 1730, 1275, 1255, 1235, 1170, 1040, 1020 cm^{-1}; ^{1}H NMR δ 3.92 (ddd, J = 10.9, 5.4, and 1.6 Hz, 1H), 3.73 (s, 3H), 3.52 (dd, J = 9.6 and 2.6 Hz, 1H), 3.48−3.41 (m, 2H), 3.15 (dq, J = 10.9 and 7.0 Hz, 1H), 3.02 (br s, 1H, OH), 1.84 (m, 1H), 1.76−1.49 (m, 4H), 1.24 (m, 1H), 1.06 (d, J = 6.6 Hz, 3H), 0.82 (d, J = 7.0 Hz, 3H), 0.81 (d, J = 6.3 Hz, 3H); ^{13}C NMR δ 176.3 (s), 76.7 (d), 75.1 (d), 65.7 (t), 51.9 (q), 40.0 (d), 35.7 (d), 31.8 (d), 27.2 (t), 25.1 (t), 17.4 (q), 14.2 (q), 8.8 (q); MS-CI$^+$ (CH_4) m/z (relative intensity) 245 (M + H$^+$, 100), 227 (29), 213 (51), 185 (19), 157 (29), 139 (12); HRMS (CI$^+$, CH_4) calcd for $C_{13}H_{25}O_4$ (M + H$^+$) 245.1753, found 245.1750.

Methyl (2*S*)-2-[(2*S*,5*S*,6*S*)-6-((1*R*)-1-Methyl-2-oxoethyl)-5-methyltetrahydro-2*H*-pyran-2-yl]propanoate (20). To a solution of **19** (50 mg, 0.21 mmol) in CH_2Cl_2 (2 mL) at 0 °C, were successively added pyridine (70 μL, 0.87 mmol, 4 equiv) and Dess−Martin periodinane (180 mg, 0.424 mmol, 2 equiv). After 3 h at rt, the reaction mixture was hydrolyzed with a mixture of a 1.5 M aqueous solution of $Na_2S_2O_3$ (7 mL) and a saturated aqueous solution of $NaHCO_3$ (7 mL). After extraction with CH_2Cl_2, the combined extracts were washed with brine, dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The residual traces of pyridine were removed from the crude material by evaporation with cyclohexane under reduced pressure and the residue was purified by flash chromatography (pentane/Et_2O 70/30) to afford 50 mg (100%) of **20** as a colorless oil: $[\alpha]^{20}_D$ +7.1 (*c* 0.7, $CHCl_3$); IR (film) 1730, 1265, 1195, 1165, 1015, 970 cm^{-1}; ^{1}H NMR δ 9.56 (d, J = 1.1 Hz, 1H), 3.91 (dd, J = 8.8 and 4.0 Hz, 1H), 3.87 (m, 1H), 3.67 (s, 3H), 3.05 (dq, J = 10.7 and 7.0 Hz, 1H), 2.56 (qdd, J = 7.0, 4.0 and 1.1 Hz, 1H), 1.79−1.55 (m, 4H), 1.32 (m, 1H), 1.07 (d, J = 7.4 Hz, 3H), 1.05 (d, J = 7.0 Hz, 3H), 0.92 (d, J = 6.6 Hz, 3H); ^{13}C NMR δ 204.4 (d), 175.4 (s), 75.3 (d), 75.0 (d), 51.7 (q), 47.8 (d), 40.6 (d), 31.1 (d), 26.6 (t), 24.7 (t), 17.6 (q), 14.2 (q), 6.3 (q); MS-CI$^+$ (CH_4) m/z (relative intensity) 243 (M + H$^+$, 58), 225 (100), 211 (60), 207 (33), 193 (48), 185 (65), 155 (45), 153 (36), 147 (27), 124 (23), 106 (35); HRMS (CI$^+$, CH_4) calcd for $C_{13}H_{23}O_4$ (M + H$^+$) 243.1596, found 243.1604.

Addition of a Chiral Crotyltitanium Reagent to Aldehyde 20. To a suspension of Cp((*R*,*R*)-TADDOL)TiCl (228 mg, 0.372 mmol, 2 equiv) in ether (3 mL) at −78 °C was added dropwise a solution of crotylmagnesium chloride (880 μL, 0.37 M in THF, 0.326 mmol, 1.75 equiv). After 30 min at −78 °C and 3 h at 0 °C, the resulting dark solution was cooled to −78 °C, and a solution of **20** (45 mg, 0.186 mmol) in ether (3 mL) was added dropwise. After 5 h at −78 °C, the reaction mixture was hydrolyzed with a 45% aqueous solution of NH_4F (2 mL). After 12 h at rt, the reaction mixture was filtered through Celite and the insoluble material was throroughly washed with ether. The organic layer was washed with brine, dried over $MgSO_4$, filtered and concentrated under reduced pressure. Analysis of the ^{1}H NMR spectrum of the crude material indicated the formation of the diastereomeric homoallylic alcohols **26** and **27** in a 70/30 ratio. Purification by flash chromatography (pentane/Et_2O 90/10) afforded 29 mg (52%) of **26** as an amorphous solid. The minor diastereomer **27** could not be efficiently separated from (*R*,*R*)-TADDOL.

Methyl (2*S*)-2-[(2*S*,5*S*,6*S*)-6-((1*S*,2*S*,3*S*)-2-Hydroxy-1,3-dimethylpent-4-enyl)-5-methyl-tetrahydro-2*H*-pyran-2-yl]propanoate (26): mp 57 °C; $[\alpha]^{20}_D$ +43.6 (*c* 1.0, $CHCl_3$); IR (CH_2Cl_2) 3540, 1740, 1720, 1640, 1280, 1260, 1170, 1120, 1085, 1020, 970, 910 cm^{-1}; ^{1}H NMR δ 5.93 (ddd, J = 16.9, 10.7, and 8.1 Hz, 1H), 5.08−5.01 (m, 2H), 3.97 (ddd, J = 11.0, 5.5, and 1.5 Hz, 1H), 3.72 (s, 3H), 3.64 (dd, J = 9.7 and 1.7 Hz, 1H), 3.38 (d, J = 6.2 Hz, 1H, OH), 3.23 (m, 1H), 3.16 (dq, J = 11.0 and 7.0 Hz, 1H), 2.36 (m, 1H), 1.82−1.52 (m, 5H), 1.24 (m, 1H), 1.08 (d, J = 7.0 Hz, 3H), 1.07 (d, J = 6.6 Hz, 3H), 0.82 (d, J = 7.0 Hz, 3H), 0.80 (d, J = 6.3 Hz, 3H); ^{13}C NMR δ 176.5 (s), 140.1 (d), 114.4 (t), 75.5 (d), 75.1 (d), 75.0 (d), 52.0 (q), 39.9 (d+d, 2C), 37.0 (d), 31.8 (d), 27.4 (t), 25.2 (t), 18.2 (q), 17.6 (q), 14.2 (q), 9.3 (q); MS-CI$^+$ (CH_4) m/z (relative intensity) 299 (M + H$^+$, 100), 281 (34), 243 (36), 213 (18), 185 (50), 135 (61), 103 (17); HRMS (CI$^+$, CH_4) calcd for $C_{17}H_{31}O_4$ (M + H$^+$) 299.2222, found 299.2227.

Methyl (2*S*)-2-[(2*S*,5*S*,6*S*)-6-((1*S*,2*R*,3*R*)-2-Hydroxy-1,3-dimethylpent-4-enyl)-5-methyl-tetrahydro-2*H*-pyran-2-yl]propanoate (27): amorphous white solid; $[\alpha]^{20}_D$ +51.7 (*c* 0.6, $CHCl_3$); IR (CH_2Cl_2) 3500, 1730, 1720, 1235, 1015, 965, 900 cm^{-1}; ^{1}H NMR δ 5.94 (ddd, J = 17.3, 10.4, and 7.4 Hz, 1H), 5.05 (ddd, J = 17.3, 1.8, and 1.1 Hz, 1H), 4.99 (ddd, J = 10.4, 1.8, and 0.7 Hz, 1H), 3.99 (ddd, J = 11.0, 5.2, and 1.8 Hz, 1H), 3.74 (s, 3H), 3.49 (dd, J = 9.7 and 2.8 Hz, 1H), 3.36 (d, J = 8.8 Hz, 1H), 3.27 (s, 1H, OH), 3.12 (dq, J = 11.0 and 6.9 Hz, 1H), 2.25 (m, 1H), 1.91−1.55 (m, 5H), 1.27 (m, 1H), 1.08 (d, J = 7.0 Hz, 3H), 0.92 (d, J = 7.0 Hz, 3H), 0.86 (d, J = 7.0 Hz, 3H), 0.83 (d, J = 6.6 Hz, 3H); ^{13}C NMR δ 175.5 (s), 142.7 (d), 113.4 (t), 82.6 (d), 79.4 (d), 75.1 (d), 51.9 (q), 41.2 (d), 39.9 (d), 34.4 (d), 31.6 (d), 26.9 (t), 24.9 (t), 17.6 (q), 16.8 (q), 14.6 (q), 4.8 (q); MS-CI$^+$ (CH_4) m/z (relative intensity) 299 (M + H$^+$, 66), 281 (44), 243 (20), 185 (100), 171 (13); HRMS (CI$^+$, CH_4) calcd for $C_{17}H_{31}O_4$ (M + H$^+$) 299.2222, found 299.2220.

Addition of the Chiral Allenylzinc (*P*)-29 to Aldehyde 20. To a solution of $Pd(OAc)_2$ (26 mg, 0.12 mmol, 0.17 equiv) in THF (20 mL) at −78 °C was added a solution of PPh_3 (30 mg, 0.12 mmol, 0.17 equiv) in THF (2 mL). After 10 min at −78 °C were successively added a solution of **20** (162 mg, 0.669

mmol, 1 equiv) and (*R*)-**28** (300 mg, 2.03 mmol, 3 equiv) in THF (5 mL) and Et_2Zn (4.0 mL, 1 M in hexanes, 4.0 mmol, 6 equiv) dropwise. After 14 h at −30 °C, the reaction mixture was poured into a saturated aqueous solution of NH_4Cl, and a 1 M aqueous solution of hydrochloric acid (10 mL) was added dropwise. After extraction with ether, the combined extracts were washed with brine, dried over $MgSO_4$, filtered and concentrated under reduced pressure. Analysis of the GC−MS and ^{1}H NMR spectra of the crude material indicated the formation of the three diastereomeric homopropargylic alcohols **30**, **31**, and **32** in a 80/12/8 ratio. Purification by flash chromatography (petroleum ether/Et_2O gradient 80/20 to 60/40) afforded 13 mg (7%) of **32** as an amorphous solid, 124 mg (63%) of **30**, and 18 mg (9%) of **31** as white solids.

Methyl (2*S*)-2-[(2*S*,5*S*,6*S*)-6-((1*S*,2*S*,3*S*)-2-Hydroxy-1,3-dimethylpent-4-ynyl)-5-methyl-tetrahydro-2*H*-pyran-2-yl]propanoate (30): R_f 0.31 (petroleum ether/EtOAc 80/20); mp 90 °C; $[\alpha]^{20}_D$ +44.2 (*c* 1.15, $CHCl_3$); IR (CH_2Cl_2) 3530, 3280, 1710, 1275, 1255, 1245, 1105, 1080, 1040, 1020, 970 cm^{-1}; ^{1}H NMR δ 3.94 (m, 1H), 3.72 (s, 3H), 3.67 (dd, J = 9.9 and 1.8 Hz, 1H), 3.49 (d, J = 6.6 Hz, 1H, OH), 3.22 (m, 1H), 3.17 (dq, J = 11.0 and 6.8 Hz, 1H), 2.67 (m, 1H), 2.05 (d, J = 2.2 Hz, 1H), 1.93 (m, 1H), 1.82−1.54 (m, 3H), 1.29 (d, J = 7.0 Hz, 3H), 1.34−1.17 (m, 2H), 1.06 (d, J = 6.6 Hz, 3H), 0.83 (d, J = 6.3 Hz, 3H), 0.82 (d, J = 7.0 Hz, 3H); ^{13}C NMR δ 176.7 (s), 85.4 (s), 75.3 (d), 74.7 (d), 73.8 (d), 69.6 (d), 52.0 (q), 39.8 (d), 38.2 (d), 31.8 (d), 29.2 (d), 27.5 (t), 25.3 (t), 18.5 (q), 17.6 (q), 14.2 (q), 9.2 (q); MS-CI$^+$ (CH_4) *m*/*z* (relative intensity) 297 (M + H$^+$, 100), 279 (13), 265 (8), 243 (23), 185 (35), 171 (7); HRMS (CI$^+$, CH_4) calcd for $C_{17}H_{29}O_4$ (M + H$^+$) 297.2068, found 297.2065.

Methyl (2*S*)-2-[(2*S*,5*S*,6*S*)-6-((1*S*,2*R*,3*R*)-2-Hydroxy-1,3-dimethylpent-4-ynyl)-5-methyltetrahydro-2*H*-pyran-2-yl]propanoate (31): R_f 0.22 (petroleum ether/EtOAc 80/20); mp 93 °C; $[\alpha]^{20}_D$ +61.4 (*c* 0.7, $CHCl_3$); IR (CH_2Cl_2) 3480, 3260, 1730, 1710, 1280, 1255, 1230, 1110, 1015, 985, 970 cm^{-1}; ^{1}H NMR δ 4.01 (m, 1H), 3.78 (s, 3H), 3.53−3.46 (m, 2H), 3.14. (d, J = 1.5 Hz, 1H, OH), 3.11 (dq, J = 11.0 and 6.9 Hz, 1H), 2.60 (dqd, apparent quintet d, J = 7.0, 2.2 Hz, 1H), 2.08 (d, J = 2.2 Hz, 1H), 1.86 (m, 1H), 1.78−1.57 (m, 3H), 1.32−1.23 (m, 2H), 1.18 (d, J = 7.0 Hz, 3H), 1.09 (d, J = 6.6 Hz, 3H), 0.91 (d, J = 7.0 Hz, 3H), 0.84 (d, J = 6.6 Hz, 3H); ^{13}C NMR δ 175.6 (s), 87.1 (s), 81.6 (d), 78.0 (d), 75.1 (d), 69.2 (d), 52.0 (q), 39.9 (d), 35.2 (d), 31.5 (d), 30.5 (d), 26.8 (t), 24.9 (t), 17.8 (q), 17.5 (q), 14.6 (q), 5.2 (q); MS-CI$^+$ (CH_4) *m*/*z* (relative intensity) 297 (M + H$^+$, 100), 279 (18), 243 (14), 185 (50); HRMS (CI$^+$, CH_4) calcd for $C_{17}H_{29}O_4$ (M + H$^+$) 297.2066, found 297.2062.

Methyl (2*S*)-2-[(2*S*,5*S*,6*S*)-6-((1*S*,2*R*,3*S*)-2-Hydroxy-1,3-dimethylpent-4-ynyl)-5-methyltetrahydro-2*H*-pyran-2-yl]propanoate (32): R_f 0.42 (petroleum ether/EtOAc 80/20); $[\alpha]^{20}_D$ +46.9 (*c* 0.6, $CHCl_3$); IR (CH_2Cl_2) 3480, 3300, 1735, 1195, 1170, 1075, 1015, 965 cm^{-1}; ^{1}H NMR δ 4.02 (m, 1H), 3.76 (s, 3H), 3.55 (dd, J = 10.1 and 2.4 Hz, 1H), 3.49 (s, 1H, OH), 3.45 (d, J = 9.9 Hz, 1H), 3.17 (dq, J = 11.2 and 6.8 Hz, 1H), 2.49 (m, 1H), 2.32 (m, 1H), 2.05 (d, J = 2.6 Hz, 1H), 1.85−1.55 (m, 3H), 1.33−1.20 (m, 2H), 1.28 (d, J = 6.6 Hz, 3H), 1.09 (d, J = 6.6 Hz, 3H), 0.86 (d, J = 7.4 Hz, 3H), 0.84 (d, J = 6.6 Hz, 3H); ^{13}C NMR δ 175.7 (s), 86.7 (s), 82.6 (d), 79.4 (d), 75.4 (d), 69.9 (d), 51.8 (q), 39.4 (d), 35.1 (d), 32.0 (d), 30.1 (d), 26.9 (t), 25.0 (t), 18.1 (q), 17.4 (q), 14.7 (q), 4.4 (q); MS-CI$^+$ (CH_4) *m*/*z* (relative intensity) 297 (M + H$^+$, 100), 279 (11), 243 (16), 185 (30); HRMS (CI$^+$, CH_4) calcd for $C_{17}H_{29}O_4$ (M + H$^+$) 297.2066, found 297.2061.

Hydrogenation of 30 and 31. To a solution of **30** (33 mg, 0.11 mmol) in toluene (1 mL) were successively added quinoline (18 μL, 0.15 mmol, 1.4 equiv) and Pd/$BaSO_4$ (38 mg, 5% Pd, 0.018 mmol, 0.16 equiv). The resulting mixture was stirred under an atmosphere of hydrogen. After 30 min, the reaction mixture was diluted with CH_2Cl_2 and filtered through Celite. The filtrate was evaporated under reduced pressure, and the crude material was purified by flash chromatography (pentane/Et_2O 80/20) to afford 31 mg (93%) of **26** as a white solid. Similarly, hydrogenation of **31** (25 mg, 0.084 mmol) followed by purification by flash chromatography (pentane/Et_2O: 80/20) afforded 12 mg (48%) of **27** as an amorphous white solid.

Methyl (2*S*)-2-((2*S*,5*S*,6*S*)-6-{(1*R*,2*S*,3*S*)-2-[(*tert*-Butyldimethylsilyl)oxy]-1,3-dimethylpent-4-enyl}-5-methyltetrahydro-2*H*-pyran-2-yl)propanoate (33). To a solution of **26** (59 mg, 0.20 mmol) in CH_2Cl_2 (5 mL) at −78 °C, were successively added 2,6-lutidine (90 μL, 0.77 mmol, 3.9 equiv) and *tert*-butyldimethylsilyl triflate (140 μL, 0.609 mmol, 3.1 equiv). After 4 h at −78 °C, the reaction mixture was poured into a saturated aqueous solution of $NaHCO_3$ and extracted with ether. The combined extracts were dried over $MgSO_4$, filtered and concentrated under reduced pressure. The crude material was purified by flash chromatography (petroleum ether/Et_2O gradient 99/1 to 95/5) to afford 71 mg (87%) of **33** as a colorless oil: $[\alpha]^{20}_D$ +28.6 (*c* 0.5, $CHCl_3$); IR (film) 3060, 1740, 1255, 1165, 1110, 1040, 1005, 860, 830, 775 cm^{-1}; ^{1}H NMR δ 5.98 (ddd, J = 17.6, 10.3, and 8.5 Hz, 1H), 4.96−4.87 (m, 2H), 3.75 (ddd, apparent td, J = 8.6 and 4.5 Hz, 1H), 3.69 (s, 3H), 3.54 (dd, J = 5.1 and 2.2 Hz, 1H), 3.39 (dd, J = 7.2 and 4.6 Hz, 1H), 2.63 (dq, J = 9.2 and 7.0 Hz, 1H), 2.29 (m, 1H), 2.06 (m, 1H), 1.79−1.68 (m, 2H), 1.61−1.47 (m, 2H), 1.39 (m, 1H), 1.08 (d, J = 7.0 Hz, 3H), 1.00 (d, J = 6.6 Hz, 6H), 0.92 (s, 9H), 0.87 (d, J = 7.4 Hz, 3H), 0.08 (s, 3H), 0.06 (s, 3H); ^{13}C NMR δ 175.9 (s), 141.8 (d), 113.3 (t), 79.2 (d), 77.5 (d), 72.1 (d), 51.6 (q), 44.5 (d), 41.0 (d), 39.1 (d), 28.4 (d), 26.0 (q, 3C), 25.7 (t), 23.9 (t), 20.5 (q), 18.4 (q), 18.3 (s), 13.5 (q), 10.2 (q), −3.9 (q), −4.5 (q); MS-CI$^+$ (CH_4) *m*/*z* (relative intensity) 413 (M + H$^+$, 100), 397 (21), 355 (11), 281 (48), 185 (79); HRMS (CI$^+$, CH_4) calcd for $C_{23}H_{45}O_4Si$ (M + H$^+$) 413.3088, found 413.3087.

Methyl (2*S*)-2-((2*S*,5*S*,6*S*)-6-{[(1*R*,2*R*,3*R*)-2-(*tert*-Butyldimethylsilyl)oxy]-1,3-dimethyl-4-oxohexyl}-5-methyltetrahydro-2*H*-pyran-2-yl)propanoate (23). To a solution of **34** (95 mg, 0.23 mmol) in acetone/water (9/1, 1.5 mL) at 0 °C were added NMO (41 mg, 0.35 mmol, 1.5 equiv) and OsO_4 (0.14 mL, 4% in water, 0.023 mmol, 0.1 equiv). Additional quantities of NMO (20 mg and 39 mg, 0.17 and 0.33 mmol, 0.7 equiv and 1.4 equiv) and OsO_4 (30 μL and 140 μL, 4% in water, 4.9 μmol and 23 μmol, 0.02 equiv and 0.1 equiv) were added after 19 h and then after 40 h. After 46 h of stirring, finely crushed $Na_2S_2O_3$ (107 mg) and Celite (396 mg) were added to the reaction mixture. After 1.5 h, the resulting mixture was filtered through glass wool, the filtrate was evaporated under reduced pressure, and the residue was dissolved in EtOAc. The resulting solution was successively washed with a 25% aqueous solution of $Na_2S_2O_3$ and brine, dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The crude intermediate diol was dissolved in THF/water (1/1, 6 mL), and $NaIO_4$ was added (120 mg, 0.561 mmol, 2.4 equiv). After 40 min at rt, the reaction mixture was extracted with ether. The combined extracts were successively washed with a 25% aqueous solution of $Na_2S_2O_3$ and brine, dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The crude aldehyde **34** was not purified and was directly engaged in the next step. EtLi·LiBr (9.0 mL, 0.46 M in ether, 4.1 mmol, 18 equiv) (prepared from EtBr and Li metal, Et_2O, 0−5 °C) was added dropwise to a suspension of CuI (398 mg, 2.09 mmol, 9 equiv) in ether (10 mL) at −78 °C. The reaction mixture was warmed to −40 °C, and after 15 min a brown homogeneous solution of the Gilman cuprate was obtained. The reaction mixture was cooled to −78 °C, and a solution of **34** in ether (4 mL) was added dropwise. After 15 min, the reaction mixture was poured into a NH_4Cl/NH_4OH mixture (pH = 8). After 1.5 h of stirring, the resulting homogeneous mixture was extracted with ether. The combined extracts were washed with brine, dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The crude intermediate secondary alcohol was dissolved in CH_2Cl_2 (10 mL), and to the resulting solution at 0 °C were successively added pyridine (80 μL, 0.99 mmol, 4.3 equiv) and Dess−Martin periodinane (222 mg, 0.523 mmol, 2.3 equiv). After 18 h at rt,

the reaction mixture was hydrolyzed with a 1.5 M aqueous solution of Na_2SO_3 (12 mL) and a saturated aqueous solution of $NaHCO_3$ (12 mL). After extraction with CH_2Cl_2, the combined extracts were washed with brine, dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The crude material was purified by flash chromatography (petroleum ether/Et_2O gradient 90/10 to 80/20) to afford 70 mg (68%, from **33**) of **23** as a colorless oil: $[\alpha]^{20}_D$ −10.8 (*c* 0.65, $CHCl_3$); IR (film) 1740, 1720, 1255, 1165, 1050, 835, 775 cm^{-1}; ^1H NMR δ 3.93 (dd, J = 7.0 and 4.0 Hz, 1H), 3.71 (s, 3H), 3.70 (m, 1H), 3.43 (dd, J = 8.5 and 3.7 Hz, 1H), 2.77 (m, 1H), 2.59 (dq, J = 8.8 and 7.0 Hz, 1H), 2.51 (q, J = 7.2 Hz, 2H), 2.13 (m, 1H), 1.87−1.72 (m, 2H), 1.54−1.38 (m, 3H), 1.08 (d, J = 7.0 Hz, 3H), 1.03 (d, J = 7.0 Hz, 3H), 1.01 (t, J = 7.2 Hz, 3H), 0.97 (d, J = 7.4 Hz, 3H), 0.89 (d, J = 7.0 Hz, 3H), 0.87 (s, 9H), 0.10 (s, 3H), 0.01 (s, 3H); ^{13}C NMR δ 213.7 (s), 175.8 (s), 78.8 (d), 75.9 (d), 71.8 (d), 51.6 (q), 49.2 (d), 44.8 (d), 39.2 (d), 36.6 (t), 28.1 (d), 25.9 (q, 3C), 25.5 (t), 23.6 (t), 18.2 (q), 18.0 (s), 13.6 (q), 13.4 (q), 9.6 (q), 7.4 (q), −4.3 (q), −4.8 (q); MS-EI *m*/*z* (relative intensity) 413 (M − Et^+, 0.2), 385 (M − *t*-Bu^+, 2), 229 (14), 186 (11), 185 (100), 173 (14), 153 (70), 125 (16), 97 (11), 75 (15), 57 (18); HRMS (CI^+, CH_4) calcd for $C_{24}H_{47}O_5Si$ (M + H^+) 443.3193, found 443.3185.

Synthesis of the C13−C25 Subunit of Zincophorin. Ethyl (*2S*)-2-[(*tert*-Butyldimethylsilyl)oxy]propanoate (38).[51] To a solution of L-ethyl lactate (14 mL, 0.12 mol) in THF (120 mL) at rt were successively added Et_3N (44 mL, 0.32 mol, 2.6 equiv), DMAP (1.55 g, 12.7 mmol, 0.1 equiv), and *tert*-butylchlorodimethylsilane (25 g, 0.17 mol, 1.3 equiv). After 24 h at rt, additional quantities of Et_3N (9.0 mL, 65 mmol, 0.5 equiv), DMAP (0.32 g, 2.6 mmol, 0.02 equiv), and *tert*-butylchlorodimethylsilane (5.0 g, 33 mmol, 0.27 equiv) were added. After 60 h, the reaction mixture was concentrated under reduced pressure, and the residue was taken up in Et_2O and filtered through Celite. The filtrate was successively washed with a 15% aqueous solution of AcOH (100 mL), water (100 mL) and a saturated aqueous solution of $NaHCO_3$ (100 mL). The organic phase was dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was distilled under reduced pressure (110 °C, 15 mmHg) to afford 24.3 g (85%) of **38** as a colorless oil: $[\alpha]^{20}_D$ −29.4 (*c* 1.44, $CHCl_3$); IR (film) 1755, 1735, 1255, 1150, 1060, 1025, 975, 830, 810, 780 cm^{-1}; ^1H NMR δ 4.31 (q, J = 6.6 Hz, 1H), 4.18 (m, 2H), 1.40 (d, J = 6.6 Hz, 3H), 1.28 (t, J = 7.2 Hz, 3H), 0.90 (s, 9H), 0.10 (s, 3H), 0.07 (s, 3H); ^{13}C NMR δ 174.1 (s), 68.4 (d), 60.7 (t), 25.7 (q, 3C), 21.3 (q), 18.3 (s), 14.2 (q), −5.0 (q), −5.3 (q); MS-EI *m*/*z* (relative intensity) 217 (M − Me^+, 2), 175 (M − *t*-Bu^+, 72), 159 (42), 147 (100), 119 (40), 103 (49), 75 (64), 73 (49), 59 (12).

(2*S*)-2-[(*tert*-Butyldimethylsilyl)oxy]propanal (37).[50] To a solution of **38** (3.00 g, 12.9 mmol) in Et_2O (50 mL) at −78 °C was added dropwise Dibal-H (15.5 mL, 1 M in hexanes, 15.5 mmol, 1.2 equiv). After 1 h at −40 °C, the reaction mixture was poured into a mixture of a saturated aqueous solution of Rochelle's salt (140 mL) and ether (100 mL) was added. After the mixture was stirred for 2 h at rt, the layers were separated and the aqueous phase was extracted with ether. The combined extracts were washed with brine, dried over $MgSO_4$, filtered, and concentrated under reduced pressure (bath temperature ≤ 20 °C) to afford 2.43 g (100%) of **37** as a colorless oil. This sensitive compound was directly engaged in the next step without purification. An analytical sample was obtained after purification by flash chromatography (petroleum ether/Et_2O: 50/50): $[\alpha]^{20}_D$ −12.6 (*c* 1.1, $CHCl_3$) (lit.[50] $[\alpha]^{19}_D$ −12.0 (*c* 1.5, $CHCl_3$)); IR (film) 2860, 2790, 1740, 1260, 1110 (br), 835, 810, 780 cm^{-1}; ^1H NMR δ 9.62 (d, J = 1.1 Hz, 1H), 4.10 (qd, J = 7.0 and 1.1 Hz, 1H), 1.28 (d, J = 7.0 Hz, 3H), 0.92 (s, 9H), 0.11 (s, 3H), 0.09 (s, 3H); ^{13}C NMR δ 204.1 (d), 73.8 (d), 25.7 (q, 3C), 18.5 (q), 18.1 (s), −4.8 (2q, 2C).

(1*R*,2*R*)-1-{(1*S*)-1-[(*tert*-Butyldimethylsilyl)oxy]ethyl}-2-methylbut-3-yn-1-ol (36).[50] To a solution of $Pd(OAc)_2$ (164 mg, 0.731 mmol, 0.073 equiv) in THF (220 mL) at −78 °C was added a solution of PPh_3 (195 mg, 0.743 mmol, 0.074 equiv) in THF (1 mL). After 10 min at −78 °C, a solution of **37** (1.88 g, 10.0 mmol) and (*S*)-**28** (2.21 g, 15.0 mmol, 1.5 equiv) in THF (10 mL) and Et_2Zn (30.0 mL, 1 M in hexanes, 30.0 mmol, 3.0 equiv) were successively added dropwise. After 14 h at −20 °C, the reaction mixture was cautiously poured into a saturated aqueous solution of NH_4Cl, and a 1 M aqueous solution of hydrochloric acid (10 mL) was added dropwise. After extraction with ether, the combined extracts were washed with brine, dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The crude material was purified by flash chromatography (petroleum ether/Et_2O gradient 90/10 at 85/15) to give 1.81 g (75%) of **36** as a colorless oil: $[\alpha]^{20}_D$ +29.6 (*c* 0.67, $CHCl_3$) (lit.[50] $[\alpha]^{20}_D$ +36.0 (*c* 2.57, $CHCl_3$)); IR (film) 3430, 3270, 1260, 1250, 1090, 1070, 1005, 940, 840, 780 cm^{-1}; ^1H NMR δ 3.76 (dq, J = 7.3 and 6.0 Hz, 1H), 3.17 (ddd, J = 8.5, 7.3, and 3.7 Hz, 1H), 2.91 (m, 1H), 2.13 (d, J = 2.6 Hz, 1H), 1.90 (d, J = 8.5 Hz, 1H, OH), 1.26 (d, J = 7.4 Hz, 3H), 1.22 (d, J = 6.0 Hz, 3H), 0.89 (s, 9H), 0.10 (s, 3H), 0.09 (s, 3H); ^{13}C NMR δ 84.9 (s), 78.6 (d), 71.1 (d), 69.9 (d), 28.5 (d), 25.8 (q, 3C), 19.6 (q), 18.0 (q), 17.9 (s), −4.3 (q), −4.9 (q); MS-EI *m*/*z* (relative intensity) 227 (M − Me^+, 0.3), 185 (M − *t*-Bu^+, 14), 173 (11), 159 (62), 141 (15), 131 (89), 119 (29), 115 (17), 103 (17), 75 (100), 73 (61).

(3*R*,4*R*,5*S*)-5-[(*tert*-Butyldimethylsilyl)oxy]-4-methoxymethoxy-3-methylhex-1-yne (39). To a solution of **36** (4.88 g, 20.1 mmol) in CH_2Cl_2 (100 mL) at 0 °C were successively added *i*-Pr_2NEt (8.50 mL, 48.8 mmol, 2.4 equiv) and MOMCl (3.70 mL, 48.7 mmol, 2.4 equiv) dropwise. After 24 h at rt, additional quantities of *i*-Pr_2NEt (0.80 mL, 4.6 mmol, 0.2 equiv) and MOMCl (0.40 mL, 5.3 mmol, 0.3 equiv) were added at 0 °C. After 14 h at rt, the reaction mixture was hydrolyzed with a saturated aqueous solution of $NaHCO_3$ and extracted with ether. The combined extracts were washed with brine, dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The crude material was purified by flash chromatography (petroleum ether/Et_2O 90/10) to afford 5.08 g (88%) of **39** as a colorless oil: $[\alpha]^{20}_D$ +26.3 (*c* 1.21, $CHCl_3$); IR (film) 3310, 3290, 3270, 1260, 1150, 1105, 1040, 1005, 835, 780 cm^{-1}; ^1H NMR δ 4.77 (d, J = 6.8 Hz, 1H), 4.73 (d, J = 6.8 Hz, 1H), 3.93 (dq, apparent quintet, J = 6.3 Hz, 1H), 3.42 (s, 3H), 3.22 (dd, J = 6.8 and 3.5 Hz, 1H), 2.90 (m, 1H), 2.07 (d, J = 2.2 Hz, 1H), 1.26 (d, J = 7.4 Hz, 3H), 1.21 (d, J = 5.9 Hz, 3H), 0.87 (s, 9H), 0.09 (s, 3H), 0.07 (s, 3H); ^{13}C NMR δ 98.2 (t), 85.8 (d+s, 2C), 69.8 (d), 69.5 (d), 56.2 (q), 28.3 (d), 25.8 (q, 3C), 20.0 (q), 18.3 (q), 17.9 (s), −4.3 (q), −4.9 (q); MS-EI *m*/*z* (relative intensity) 255 (M − OMe^+, 0.1), 233 (M − $CH(CH_3)$-$C{\equiv}CH^+$, 3), 197 (15), 159 (46), 131 (100), 123 (14), 115 (17), 103 (16), 89 (45), 75 (25), 73 (52), 59 (12). Anal. Calcd for $C_{15}H_{30}O_3Si$: C, 62.89; H, 10.55. Found: C, 62.90; H, 10.69.

(6*R*,7*R*,8*S*)-1-Benzyloxy-8-[(*tert*-butyldimethylsilyl)oxy]-7-methoxymethoxy-6-methylnon-4-yne (40). To a solution of **39** (1.49 g, 5.20 mmol) in THF (30 mL) at −78 °C was added dropwise *n*-BuLi (2.70 mL, 2.5 M in hexanes, 6.75 mmol, 1.3 equiv). The reaction mixture was warmed to −50 °C, stirred for 5 min, and cooled again to −78 °C. A solution of 1-benzyloxy-3-bromopropane (1.20 mL, 6.80 mmol, 1.3 equiv) in THF (10 mL) and HMPA (4.80 mL, 27.6 mmol, 5.3 equiv) were successively added. After 1.5 h at rt, the reaction mixture was poured into a saturated aqueous solution of NH_4Cl and extracted with ether. The combined extracts were washed with brine, dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The crude material was purified by flash chromatography (petroleum ether/EtOAc gradient 95/5 to 90/10) to give 2.22 g (98%) of **40** as a colorless oil: $[\alpha]^{20}_D$ +8.3 (*c* 1.0, $CHCl_3$); IR (film) 1255, 1155, 1105, 1035, 920, 830, 810, 780, 740, 700 cm^{-1}; ^1H NMR δ 7.36−7.25 (m, 5H), 4.79 (d, J = 6.6 Hz, 1H), 4.74 (d, J = 6.6 Hz, 1H), 4.52 (s, 2H), 3.94 (dq, apparent quintet, J = 6.3 Hz, 1H), 3.57 (t, J = 6.4 Hz, 2H), 3.44 (s, 3H), 3.24 (dd, J = 6.3 and 4.0 Hz, 1H), 2.83 (m, 1H), 2.31 (td, J = 7.2 and 2.2 Hz, 2H), 1.81 (m, 2H), 1.21 (d, J = 5.9 Hz, 3H), 1.21 (d, J = 7.0 Hz, 3H), 0.89 (s, 9H), 0.10 (s,

3H), 0.08 (s, 3H); ^{13}C NMR δ 138.6 (s), 128.3 (d, 2C), 127.6 (d, 2C), 127.5 (d), 98.1 (t), 85.8 (d), 81.8 (s), 81.1 (s), 72.9 (t), 69.7 (d), 69.1 (t), 56.1 (q), 29.2 (t), 28.4 (d), 25.8 (q, 3C), 19.7 (q), 18.7 (q), 18.0 (s), 15.8 (t), −4.3 (q), −4.9 (q); MS-EI *m/z* (relative intensity) 404 (M − CH_2=$O^{+\bullet}$, 0.1), 377 (M − *t*-Bu^+, 0.1), 225 (16), 201 (14), 159 (39), 131 (53), 125 (17), 115 (15), 103 (13), 91 (100), 89 (19), 75 (14). Anal. Calcd for $C_{25}H_{42}O_4Si$: C, 69.08; H, 9.74. Found: C, 68.99; H, 9.76.

(2*S*,3*R*,4*R*)-9-Benzyloxy-3-methoxymethoxy-4-methylnon-5-yn-2-ol (41). To a solution of **40** (4.28 g, 9.84 mmol) in THF (50 mL) at 0 °C was added *n*-Bu_4NF (30 mL, 1 M in THF, 30 mmol, 3 equiv). After 16 h at rt, the reaction mixture was hydrolyzed with a saturated aqueous solution of NH_4Cl and extracted with ether. The combined extracts were dried over $MgSO_4$, filtered, and concentrated under reduced pressure to give 3.15 g (100%) of **41**, which was directly engaged in the next step without further purification. An analytical sample was obtained after purification by flash chromatography (petroleum ether/EtOAc 60/40): $[\alpha]^{20}_D$ −28.5 (*c* 0.98, $CHCl_3$); IR (film) 3420, 1155, 1100, 1075, 1030, 740, 700 cm^{-1}; ^{1}H NMR δ 7.37−7.27 (m, 5H), 4.79 (d, *J* = 6.8 Hz, 1H), 4.73 (d, *J* = 6.8 Hz, 1H), 4.53 (s, 2H), 3.89 (m, 1H), 3.57 (t, *J* = 6.3 Hz, 2H), 3.45 (s, 3H), 3.39 (dd, *J* = 6.3 and 4.0 Hz, 1H), 3.22 (m, 1H), 2.69 (m, 1H), 2.32 (td, *J* = 7.0 and 2.2 Hz, 2H), 1.81 (m, 2H), 1.22 (d, *J* = 6.3 Hz, 3H), 1.18 (d, *J* = 7.0 Hz, 3H); ^{13}C NMR δ 138.4 (s), 128.2 (d, 2C), 127.4 (d+d, 2C+1C), 98.2 (t), 87.2 (d), 81.8 (s), 81.4 (s), 72.8 (t), 68.8 (t), 67.4 (d), 55.9 (q), 29.0 (t), 28.6 (d), 17.8 (q), 17.7 (q), 15.5 (t); MS-EI *m/z* (relative intensity) 275 (M − CH_2OMe^+, 1), 201 (12), 167 (7), 155 (8), 125 (13), 123 (12), 95 (13), 91 (100), 87 (12). Anal. Calcd for $C_{19}H_{28}O_4$: C, 71.22; H, 8.81. Found: C, 71.07; H, 9.00.

(3*R*,4*R*)-9-Benzyloxy-3-methoxymethoxy-4-methylnon-5-yn-2-one (35). To a solution of **41** (3.15 g, 9.84 mmol) in CH_2Cl_2 (80 mL) at 0 °C were successively added pyridine (3.20 mL, 39.6 mmol, 4 equiv) and Dess−Martin periodinane (8.43 g, 19.9 mmol, 2 equiv). After 4.5 h at rt, the reaction mixture was hydrolyzed with a saturated aqueous solution of $NaHCO_3$ and extracted with ether. The combined extracts were washed with a 25% aqueous solution of $Na_2S_2O_3$, dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The residual traces of pyridine were removed by evaporation with cyclohexane under reduced pressure, and the residue was purified by flash chromatography (petroleum ether/EtOAc gradient 85/15 to 75/25) to afford 2.89 g (92% from **40**) of **35** as a colorless oil: $[\alpha]^{20}_D$ +31.0 (*c* 1.35, $CHCl_3$); IR (film) 1720, 1215, 1150, 1110, 1075, 1035, 945, 920, 740, 700 cm^{-1}; ^{1}H NMR δ 7.38−7.25 (m, 5H), 4.72 (d, AB syst., *J* = 6.6 Hz, 1H), 4.68 (d, AB syst., *J* = 6.6 Hz, 1H), 4.51 (s, 2H), 3.90 (d, *J* = 4.8 Hz, 1H), 3.54 (t, *J* = 6.3 Hz, 2H), 3.41 (s, 3H), 2.91 (m, 1H), 2.30 (td, *J* = 7.2 and 2.3 Hz, 2H), 2.24 (s, 3H), 1.78 (m, 2H), 1.20 (d, *J* = 7.0 Hz, 3H); ^{13}C NMR δ 208.8 (s), 138.5 (s), 128.3 (d, 2C), 127.5 (d+d, 2C+1C), 96.9 (t), 85.2 (d), 82.3 (s), 79.9 (s), 72.9 (t), 68.8 (t), 56.2 (q), 29.3 (d), 29.0 (t), 27.2 (q), 17.6 (q), 15.6 (t); MS-EI *m/z* (relative intensity) 273 (M − CH_2-OMe^+, 9), 201 (9), 153 (7), 109 (6), 95 (7), 92 (9), 91 (100). Anal. Calcd for $C_{19}H_{26}O_4$: C, 71.67; H, 8.23. Found: C, 71.71; H, 8.25.

(2*Z*)-(4*R*,5*R*,6*R*)-11-Benzyloxy-5-methoxymethoxy-4,6-dimethylundec-2-en-7-yn-4-ol (42) and (2*Z*)-(4*S*,5*R*,6*R*)-11-Benzyloxy-5-methoxymethoxy-4,6-dimethylundec-2-en-7-yn-4-ol (42′). To a suspension of $MgBr_2$·OEt_2 (5.30 g, 20.5 mmol, 7.5 equiv) in THF (50 mL) at −78 °C was added a solution of (*Z*)-prop-1-enyllithium [prepared from (*Z*)-1-bromoprop-1-ene (12 g, 99 mmol) and Li (1.70 g, 245 mmol, 2.5 equiv) in Et_2O (70 mL) at 0−5 °C] (12.5 mL, 1.2 M in Et_2O, 15.0 mmol, 5.6 equiv). The reaction mixture was warmed to rt, stirred for 30 min, and cooled to −78 °C. A solution of **35** (860 mg, 2.70 mmol) in THF (15 mL) was added dropwise, and after 1.25 h at −78 °C, the reaction mixture was poured into a saturated aqueous solution of NH_4Cl and extracted with ether. The combined extracts were dried over Na_2SO_4, filtered, and concentrated under reduced pressure. Analysis of the ^{1}H NMR spectrum of the crude material indicated the formation of a 9/1 diastereomeric mixture of the two tertiary allylic alcohols **42** and **42′**. The crude material was purified by flash chromatography (petroleum ether/EtOAc: 80/20) to give 903 mg (93%) of a mixture of **42** and **42′** (**42**/**42′** = 9/1) as a colorless oil. An analytical sample of the pure separated major diastereomer **42** was used for characterization: $[\alpha]^{20}_D$ −25.9 (*c* 1.3, $CHCl_3$); IR (film) 3450, 1650, 1150, 1100, 1035, 920, 740, 700 cm^{-1}; ^{1}H NMR δ 7.36−7.26 (m, 5H), 5.56 (dq, *J* = 11.8 and 7.2 Hz, 1H), 5.39 (apparent br d, *J* = 11.8 Hz, 1H), 4.87 (d, *J* = 6.8 Hz, 1H), 4.74 (d, *J* = 6.8 Hz, 1H), 4.52 (s, 2H), 3.56 (t, *J* = 6.4 Hz, 2H), 3.48 (s, 3H), 3.47 (m, 1H, OH), 3.38 (d, *J* = 2.6 Hz, 1H), 2.81 (m, 1H), 2.30 (td, *J* = 7.2 and 2.3 Hz, 2H), 1.89 (dd, *J* = 7.2 and 1.7 Hz, 3H), 1.80 (m, 2H), 1.46 (s, 3H), 1.24 (d, *J* = 7.0 Hz, 3H); ^{13}C NMR δ 138.5 (s), 133.8 (d), 128.3 (d, 2C), 127.6 (d, 2C), 127.5 (d), 127.4 (d), 99.2 (t), 89.9 (d), 82.3 (s), 81.4 (s), 76.0 (s), 72.9 (t), 69.0 (t), 56.2 (q), 29.1 (t), 28.2 (d), 25.1 (q), 20.6 (q), 15.8 (t), 14.5 (q); MS-EI *m/z* (relative intensity) 201 (M − $C_3H_5C(CH_3)(OH)CH(OMOM)^+$, 5), 189 (5), 109 (12), 91 (100), 85 (30). Anal. Calcd for $C_{22}H_{32}O_4$: C, 73.30; H, 8.95. Found: C, 73.31; H, 9.12.

(1*R*,2*R*,3*R*)-8-Benzyloxy-2-methoxymethoxy-1,3-dimethyl-1-((*Z*)-prop-1-enyl)oct-4-ynyl 2-Oxobutanoate (43) and (1*S*,2*R*,3*R*)-8-Benzyloxy-2-methoxymethoxy-1,3-dimethyl-1-((*Z*)-prop-1-enyl)oct-4-ynyl 2-Oxobutanoate (43′). To a solution of **42** and **42′** (9/1 ratio, 677 mg, 1.88 mmol) in THF (20 mL) were successively added DMAP (32 mg, 0.26 mmol, 0.14 equiv) and diketene (stabilized with $CuSO_4$) (0.19 mL, 2.5 mmol, 1.3 equiv). After 30 min at rt, an additional quantity of diketene was added (0.19 mL, 2.5 mmol, 1.3 equiv). After 30 min at rt, the reaction mixture was hydrolyzed with a 0.3% aqueous solution of NaOH and extracted with ether. The combined extracts were dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The crude material was purified by flash chromatography (petroleum ether/EtOAc gradient 85/15 to 75/25) to afford 67 mg (8%) of **43′** and 737 mg (88%) of **43** as colorless oils. Major diastereomer **43**: $[\alpha]^{20}_D$ +1.92 (*c* 1.0, $CHCl_3$); IR (film) 1740, 1720, 1640, 1150, 1110, 1035, 740, 700 cm^{-1}; ^{1}H NMR [only the signals corresponding to the major ketone tautomer (85%) are indicated] δ 7.36−7.25 (m, 5H), 5.64−5.53 (m, 2H), 4.86 (d, *J* = 7.0 Hz, 1H), 4.73 (d, *J* = 7.0 Hz, 1H), 4.50 (s, 2H), 3.76 (d, *J* = 1.8 Hz, 1H), 3.55 (t, *J* = 6.3 Hz, 2H), 3.44 (s, 3H), 3.39 (s, 2H), 2.78 (m, 1H), 2.29 (td, *J* = 7.0 and 2.2 Hz, 2H), 2.26 (s, 3H), 1.82 (s, 3H), 1.84−1.70 (m, 2H), 1.73 (d, *J* = 5.5 Hz, 3H), 1.25 (d, *J* = 7.0 Hz, 3H); ^{13}C NMR [only the signals corresponding to the major ketone tautomer (85%) are indicated] δ 200.6 (s), 164.9 (s), 138.5 (s), 130.6 (d), 128.3 (d, 2C), 127.7 (d), 127.5 (d+d, 2C+1C), 98.3 (t), 87.7 (s), 84.3 (d), 82.3 (s), 81.2 (s), 73.0 (t), 69.0 (t), 56.1 (q), 50.8 (t), 30.1 (q), 29.1 (t), 27.8 (d), 21.3 (q), 20.3 (q), 15.8 (t), 14.5 (q); MS-CI$^+$ (NH_3) *m/z* (relative intensity) 462 (M + NH_4^+, 92), 418 (17), 378 (42), 360 (100), 144 (15). Anal. Calcd for $C_{26}H_{36}O_6$: C, 70.24; H, 8.16. Found: C, 70.02; H, 8.34. Minor diastereomer **43′**: $[\alpha]^{20}_D$ +0.02 (*c* 1.1, $CHCl_3$); IR (film) 1740, 1720, 1645, 1245, 1150, 1105, 1035, 940, 920, 740, 700 cm^{-1}; ^{1}H NMR [only the signals corresponding to the major ketone tautomer (90%) are indicated] δ 7.38−7.24 (m, 5H), 5.70 (dq, *J* = 12.0 and 1.7 Hz, 1H), 5.55 (dq, *J* = 12.0 and 7.2 Hz, 1H), 4.71 (s, 2H), 4.50 (s, 2H), 3.75 (d, *J* = 1.8 Hz, 1H), 3.56 (t, *J* = 6.3 Hz, 2H), 3.41 (s, 2H), 3.40 (s, 3H), 2.89 (m, 1H), 2.29 (td, *J* = 7.4 and 2.2 Hz, 2H), 2.26 (s, 3H), 1.83−1.67 (m, 2H), 1.76 (s, 3H), 1.73 (dd, *J* = 7.2 and 1.7 Hz, 3H), 1.27 (d, *J* = 7.0 Hz, 3H); ^{13}C NMR [only the signals corresponding to the major ketone tautomer (90%) are indicated] δ 200.5 (s), 165.2 (s), 138.5 (s), 131.9 (d), 128.3 (d, 2C), 127.5 (d+d, 2C+1C), 126.2 (d), 98.2 (t), 85.9 (s), 84.0 (d), 81.8 (s), 81.6 (s), 72.9 (t), 69.0 (t), 56.0 (q), 50.6 (t), 30.2 (q), 29.1 (t), 27.2 (d), 21.2 (q), 21.1 (q), 15.7 (t), 14.3 (q); MS-CI$^+$ (NH_3) *m/z* (relative intensity) 462 (M + NH_4^+, 55), 418 (17), 360 (100), 343 (12), 311 (18), 281 (24), 215 (14), 191 (12); HRMS (CI$^+$, NH_3) calcd for $C_{26}H_{40}O_6N$ (M + NH_4^+) 462.2856, found 462.2853.

Carroll−Claisen Rearrangement of 43. To a solution of **43** (552 mg, 1.24 mmol) in CH_2Cl_2 (30 mL) was added neutral alumina (17 g). The solvent was evaporated under reduced pressure, and the resulting dry powder was stirred at 60 °C. After 12 h, the solid reaction mixture was suspended in EtOAc, filtered through Celite, and thoroughly washed with EtOAc. The filtrate was evaporated under reduced pressure, and analysis of the GC−MS and ^{1}H NMR spectra of the crude material indicated the formation of compounds **44**, **45**, and **46** in a 4/92/4 ratio. The crude material was purified by flash chromatography (petroleum ether/EtOAc gradient 90/10 to 80/20) to afford 37 mg (9%) of **44**, 17 mg (3%) of **46** and 305 mg (61%) of **45** as colorless oils.

(6*R*,7*R*,9*Z*)-1-Benzyloxy-7-methoxymethoxy-6-methyl-8-methyleneundec-9-en-4-yne (44): R_f 0.76 (petroleum ether/EtOAc 70/30); $[\alpha]^{20}_D$ +77.1 (*c* 0.67, $CHCl_3$); IR (film) 1150, 1100, 1030, 920, 740, 700 cm^{-1}; (this compound appeared to be slighlty contaminated by an inseparable and unindentified impurity) ^{1}H NMR δ 7.36−7.24 (m, 5H), 5.84 (apparent br d, J = 11.8 Hz, 1H), 5.74 (dq, J = 11.8 and 6.6 Hz, 1H), 5.29 (d, J = 1.8 Hz, 1H), 5.17 (br s, 1H), 4.70 (d, J = 6.8 Hz, 1H), 4.56 (d, J = 6.8 Hz, 1H), 4.50 (s, 2H), 3.87 (d, J = 8.5 Hz, 1H), 3.56 (t, J = 6.3 Hz, 2H), 3.43 (s, 3H), 2.60 (m, 1H), 2.30 (td, J = 7.0 and 2.2 Hz, 2H), 1.84−1.69 (m, 2H), 1.80 (dd, apparent br d, J = 6.6 and 1.5 Hz, 3H), 1.05 (d, J = 7.0 Hz, 3H); ^{13}C NMR δ 141.4 (s), 138.5 (s), 128.8 (d), 128.3 (d, 2C), 127.5 (d, 2C), 127.4 (d), 125.9 (d), 118.2 (t), 93.6 (t), 82.9 (d), 82.7 (s), 80.5 (s), 72.9 (t), 69.0 (t), 55.5 (q), 30.2 (d), 29.2 (t), 17.9 (q), 15.7 (t), 14.8 (q); MS-CI$^+$ (NH_3) *m*/*z* (relative intensity) 360 (M + NH_4^+, 80), 325 (19), 311 (22), 281 (23), 279 (26), 219 (26), 215 (37), 205 (21), 107 (100), 91 (24); HRMS (CI$^+$, NH_3) calcd for $C_{22}H_{34}O_3N$ (M + NH_4^+) 360.2539, found 360.2532.

(4*S*,5*Z*,7*R*,8*R*)-13-Benzyloxy-7-methoxymethoxy-4,6,8-trimethyltridec-5-en-9-yn-2-one (45): R_f 0.50 (petroleum ether/EtOAc 70/30); $[\alpha]^{20}_D$ + 1.1 (*c* 1.15, $CHCl_3$); IR (film) 1715, 1150, 1095, 1030, 920, 740, 700 cm^{-1}; ^{1}H NMR δ 7.35−7.25 (m, 5H), 5.18 (br d, J = 9.6 Hz, 1H), 4.61 (d, J = 6.6 Hz, 1H), 4.51 (d, J = 6.6 Hz, 1H), 4.50 (s, 2H), 3.71 (d, J = 9.2 Hz, 1H), 3.55 (t, J = 6.4 Hz, 2H), 3.41 (s, 3H), 2.99 (m, 1H), 2.61 (m, 1H), 2.38 (d, J = 7.0 Hz, 2H), 2.29 (td, J = 7.2 and 2.2 Hz, 2H), 2.09 (s, 3H), 1.79 (m, 2H), 1.56 (d, J = 1.5 Hz, 3H), 0.99 (d, J = 7.0 Hz, 3H), 0.95 (d, J = 7.0 Hz, 3H); ^{13}C NMR δ 207.7 (s), 138.6 (s), 136.2 (d), 131.2 (s), 128.3 (d, 2C), 127.6 (d, 2C), 127.5 (d), 93.0 (t), 84.9 (d), 83.1 (s), 80.2 (s), 72.9 (t), 69.1 (t), 55.4 (q), 50.7 (t), 30.5 (q), 29.2 (t), 29.1 (d), 28.6 (d), 20.8 (q), 18.0 (q), 15.7 (t), 10.8 (q); MS-EI *m*/*z* (relative intensity) 339 (M − OMOM$^+$, 0.4), 200 (13), 199 (100), 141 (16), 137 (29), 125 (34), 121 (12), 109 (25), 95 (12), 91 (67). Anal. Calcd for $C_{25}H_{36}O_4$: C, 74.96; H, 9.06. Found: C, 74.79; H, 9.25.

(4*R*,5*E*,7*R*,8*R*)-13-Benzyloxy-7-methoxymethoxy-4,6,8-trimethyltridec-5-en-9-yn-2-one (46): R_f 0.56 (petroleum ether/EtOAc 70/30); $[\alpha]^{20}_D$ + 35.0 (*c* 0.50, $CHCl_3$); IR (film) 1715, 1150, 1095, 1035, 740, 700 cm^{-1}; ^{1}H NMR δ 7.36−7.25 (m, 5H), 5.28 (apparent br d, J = 10.1 Hz, 1H), 4.57 (d, J = 6.8 Hz, 1H), 4.53 (d, J = 6.8 Hz, 1H), 4.51 (s, 2H), 4.35 (d, J = 9.6 Hz, 1H), 3.57 (t, J = 6.3 Hz, 2H), 3.43 (s, 3H), 3.03 (m, 1H), 2.63 (m, 1H), 2.35 (d, J = 6.6 Hz, 2H), 2.31 (td, J = 7.2 and 2.0 Hz, 2H), 2.12 (s, 3H), 1.81 (m, 2H), 1.58 (d, J = 1.5 Hz, 3H), 1.02 (d, J = 7.4 Hz, 3H), 0.98 (d, J = 6.6 Hz, 3H); ^{13}C NMR δ 207.6 (s), 138.6 (s), 137.0 (d), 130.6 (s), 128.3 (d, 2C), 127.6 (d, 2C), 127.5 (d), 93.1 (t), 83.1 (s), 80.3 (s), 76.2 (d), 72.9 (t), 69.1 (t), 55.3 (q), 50.9 (t), 30.8 (q), 29.2 (t), 29.1 (d), 28.1 (d), 21.1 (q), 17.8 (q), 17.4 (q), 15.8 (t); MS-CI$^+$ (NH_3) *m*/*z* (relative intensity) 418 (M + NH_4^+, 100), 369 (13), 340 (20), 339 (72), 277 (11), 215 (24), 199 (26), 91 (16); HRMS (CI$^+$, NH_3) calcd for $C_{25}H_{40}O_4N$ (M + NH_4^+) 418.2957, found 418.2961.

(2*RS*,4*R*,5*E*,7*R*,8R)-13-Benzyloxy-7-methoxymethoxy-4,6,8-trimethyltridec-5-en-9-yn-2-ol (47). To a solution of **45** (1.11 g, 2.77 mmol) in ether (30 mL) at −78 °C was added Dibal-H (3.4 mL, 1 M in hexanes, 3.4 mmol, 1.3 equiv). After 2 h at −78 °C, the reaction mixture was poured into a saturated aqueous solution of Rochelle's salt (50 mL) and ether was added (50 mL). After 2 h of stirring at rt, the layers were separated and the aqueous phase was extracted with ether. The combined extracts were dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The crude material was purified by flash chromatography (petroleum ether/ether 50/50) to give 1.10 g (98%) of **47** as a pale yellow oil and as a 55/45 mixture of two diastereomers: IR (film) 3400, 1360, 1145, 1085, 1020, 910, 735, 700 cm^{-1}; major diastereomer: ^{1}H NMR δ 7.40−7.25 (m, 5H), 5.27 (dd, J = 9.7 and 0.9 Hz, 1H), 4.62 (d, J = 6.6 Hz, 1H), 4.52 (d, J = 6.6 Hz, 1H), 4.51 (s, 2H), 3.81−3.67 (m, 1H), 3.75 (d, J = 9.2 Hz, 1H), 3.56 (t, J = 6.3 Hz, 2H), 3.42 (s, 3H), 2.74−2.51 (m, 2H), 2.30 (td, J = 7.2 and 2.1 Hz, 2H), 1.79 (apparent quintet, J = 6.6 Hz, 2H), 1.56 (d, J = 5.9 Hz, 3H), 1.60−1.20 (m, 2H), 1.16 (d, J = 6.3 Hz, 3H), 1.00 (d, J = 7.0 Hz, 3H), 0.99 (d, J = 6.6 Hz, 3H); ^{13}C NMR δ 138.5 (s), 138.0 (d), 130.8 or 130.4 (s), 128.3 (d, 2C), 127.6 (d, 2C), 127.5 (d), 93.0 (t), 85.0 (d), 83.1 (s), 80.3 (s), 72.9 (t), 69.1 (t), 66.7 (d), 55.4 (q), 46.8 (t), 29.7 (d), 29.2 (d), 29.2 (t), 24.3 or 23.5 (q), 21.1 or 21.5 (q), 18.1 (q), 15.7 (t), 10.8 (q); MS-EI *m*/*z* (relative intensity) 325 (M − Ph$^+$, 1), 281 (M − CH_2OBn^+, 1), 253 (M − $(CH_2)_3OBn^+$, 1), 201 (25), 169 (36), 140 (11), 139 (100), 95 (15), 91 (61), 69 (11); minor diastereomer: ^{1}H NMR δ 7.40−7.25 (m, 5H), 5.19 (dd, J = 9.6 and 1.1 Hz, 1H), 4.63 (d, J = 6.6 Hz, 1H), 4.52 (d, J = 6.6 Hz, 1H), 4.51 (s, 2H), 3.81−3.67 (m, 1H), 3.76 (d, J = 9.2 Hz, 1H), 3.56 (t, J = 6.3 Hz, 2H), 3.42 (s, 3H), 2.74−2.51 (m, 2H), 2.30 (td, J = 7.2 and 2.1 Hz, 2H), 1.79 (apparent quintet, J = 6.6 Hz, 2H), 1.55 (d, J = 5.9 Hz, 3H), 1.60−1.20 (m, 2H), 1.17 (d, J = 6.3 Hz, 3H), 1.01 (d, J = 7.0 Hz, 3H), 0.98 (d, J = 6.6 Hz, 3H);^{13}C NMR δ 138.5 (s), 137.8 (d), 130.4 or 130.8 (s), 128.3 (d, 2C), 127.6 (d, 2C), 127.5 (d), 93.0 (t), 85.1 (d), 83.0 (s), 80.2 (s), 72.9 (t), 69.1 (t), 66.3 (d), 55.4 (q), 46.8 (t), 29.2 (d), 29.2 (t), 29.1 (d), 23.5 or 24.3 (q), 21.5 or 21.1 (q), 18.1 (q), 15.7 (t), 10.8 (q); MS-EI *m*/*z* (relative intensity) 325 (M − Ph$^+$, 1), 253 (M − $(CH_2)_3OBn^+$, 1), 249 (3), 201 (23), 169 (36), 140 (10), 139 (100), 121 (10), 95 (14), 91 (63), 69 (12). Anal. Calcd for $C_{25}H_{38}O_4$: C, 74.59; H, 9.51. Found: C, 74.58; H, 9.56.

(6*R*,7*R*,8*E*,10*R*)-1-Benzyloxy-7-methoxymethoxy-6,8,10-trimethyltridec-8-en-4-yne (49). To a solution of **47** (345 mg, 0.857 mmol) in CH_2Cl_2 (10 mL) at 0 °C, were successively added *i*-Pr_2NEt (0.45 mL, 2.6 mmol, 3 equiv) and methanesulfonyl chloride (0.15 mL, 1.9 mmol, 2.3 equiv). After 2 h at 0 °C, the reaction mixture was hydrolyzed with a saturated aqueous solution of $NaHCO_3$ and extracted with ether. The combined extracts were washed with brine, dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The crude mesylate **48** was dissolved in THF (7 mL), and the resulting solution was added to a suspension of $LiAlH_4$ (129 mg, 3.40 mmol, 4 equiv) in THF (10 mL). After 3 h at reflux, the reaction mixture was cooled to 0 °C and successively cautiously treated with water (0.13 mL), a 15% aqueous solution of NaOH (0.13 mL), and water (0.39 mL). Ether was added, and after 12 h of stirring at rt, the resulting suspension was filtered through Celite. The insoluble salts were washed with boiling THF, and the filtrate was evaporated under reduced pressure. The crude material was purified by flash chromatography (petroleum ether/Et_2O 90/10, 70/30) to give 291 mg (88% from **47**) of **49** as a colorless oil: $[\alpha]^{20}_D$ +6.8 (*c* 0.97, $CHCl_3$); IR (film) 1150, 1100, 1030, 920, 740, 700 cm^{-1}; ^{1}H NMR δ 7.35−7.24 (m, 5H), 5.19 (apparent br d, J = 9.6 Hz, 1H), 4.64 (d, J = 6.6 Hz, 1H), 4.51 (d, J = 6.6 Hz, 1H), 4.50 (s, 2H), 3.74 (d, J = 9.2 Hz, 1H), 3.56 (t, J = 6.3 Hz, 2H), 3.42 (s, 3H), 2.63 (m, 1H), 2.41 (m, 1H), 2.30 (td, J = 7.0 and 2.1 Hz, 2H), 1.79 (m, 2H), 1.50 (d, J = 1.1 Hz, 3H), 1.31−1.13 (m, 4H), 1.00 (d, J = 7.0 Hz, 3H), 0.94 (d, J = 6.6 Hz, 3H), 0.86 (br t, apparent m, 3H); ^{13}C NMR δ 138.9 (d), 138.5 (s), 129.6 (s), 128.3 (d, 2C), 127.5 (d, 2C), 127.4 (d), 92.8 (t), 85.2 (d), 83.3 (s), 80.0 (s), 72.9 (t), 69.0 (t), 55.3 (q), 39.6 (t), 31.9 (d), 29.2 (t), 29.1 (d), 21.1 (q), 20.6 (t), 18.1 (q), 15.7 (t), 14.1 (q), 10.6 (q); MS-EI *m*/*z* (relative intensity) 325 (M − OMOM$^+$, 0.3), 186 (12), 185 (100), 155 (8), 139 (24), 91 (41). Anal. Calcd for $C_{25}H_{38}O_3$: C, 77.68; H, 9.91. Found: C, 77.57; H, 10.02.

(6*R*,7*R*,8*E*,10*R*)-1-Benzyloxy-6,8,10-trimethyltridec-8-en-4-yn-7-ol (50). To a solution of **49** (260 mg, 0.673 mmol) in MeOH (10 mL) at rt was added *p*-toluenesulfonic acid monohydrate (130 mg, 0.683 mmol, 1 equiv). After 4 days at rt, the reaction mixture was neutralized by addition of solid $NaHCO_3$ and evaporated under reduced pressure. The residue was taken up in water and extracted with ether. The combined extracts were washed with brine, dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The crude material was purified by flash chromatography (petroleum ether/ether: 75/25) to afford 195 mg (85%) of **50** as a colorless oil: $[\alpha]^{20}_D$ −43.5 (*c* 0.6, $CHCl_3$); IR (film) 3420, 1105, 1035, 740, 700 cm^{-1}; ^1H NMR δ 7.36−7.24 (m, 5H), 5.17 (apparent br d, J = 9.6 Hz, 1H), 4.52 (s, 2H), 3.68 (dd, J = 8.5 and 2.6 Hz, 1H), 3.56 (t, J = 6.1 Hz, 2H), 2.59 (m, 1H), 2.45−2.28 (m, 2H), 2.32 (td, J = 7.4 and 2.2 Hz, 2H), 1.80 (m, 2H), 1.58 (d, J = 1.5 Hz, 3H), 1.31−1.14 (m, 4H), 1.02 (d, J = 7.0 Hz, 3H), 0.95 (d, J = 7.0 Hz, 3H), 0.86 (br t, apparent m, 3H); ^{13}C NMR δ 138.5 (s), 136.3 (d), 132.2 (s), 128.4 (d, 2C), 127.6 (d, 2C), 127.5 (d), 82.5 (s), 81.8 (s), 81.7 (d), 73.0 (t), 68.9 (t), 39.8 (t), 31.8 (d), 31.4 (d), 29.2 (t), 20.9 (q), 20.6 (t), 17.8 (q), 15.7 (t), 14.2 (q), 10.9 (q); MS-CI$^+$ (CH_4) *m*/*z* (relative intensity) 343 (M + H^+, 11), 341 (14), 326 (28), 325 (100), 234 (22), 233 (38), 201 (15), 161 (35), 141 (17), 111 (31), 91 (47); HRMS (CI$^+$, CH_4) calcd for $C_{23}H_{35}O_2$ (M + H^+) 343.2637, found 343.2632.

(4*E*,6*R*,7*R*,8*E*,10*R*)-1-Benzyloxy-6,8,10-trimethyltrideca-4,8-dien-7-ol (51). To a suspension of $LiAlH_4$ (135 mg, 3.56 mmol, 11 equiv) in THF (20 mL) at 0 °C was added a solution of **50** (110 mg, 0.321 mmol) in THF (2 mL). The reaction mixture was heated at reflux, and additional quantities of $LiAlH_4$ (100 mg and 70 mg, 2.63 and 1.84 mmol, 8 equiv and 6 equiv) were added after 24 h and then after 24 h. After 72 h, the reaction mixture was cooled to 0 °C and cautiously successively treated with water (280 μL), a 15% aqueous solution of NaOH (280 μL), and water (840 μL). Ether (100 mL) was added, and after 3 h of stirring at rt, the resulting mixture was filtered through Celite. The insoluble salts were washed with boiling THF, and the filtrate was evporated under reduced pressure. The crude material was purified by flash chromatography (petroleum ether/ether 75/25) to afford 68 mg (61%) of **51** as a colorless oil: $[\alpha]^{20}_D$ −4.5 (*c* 0.4, $CHCl_3$); IR (film) 3440, 1100, 1015, 970, 735, 700 cm^{-1}; ^1H NMR δ 7.38−7.25 (m, 5H), 5.59 (dt, J = 15.1 and 6.8 Hz, 1H,), 5.30 (ddt, J = 15.1, 8.7 and 1.3 Hz, 1H), 5.13 (dm, J = 9.6 Hz, 1H), 4.50 (s, 2H), 3.53 (dd, J = 8.8 and 1.8 Hz, 1H), 3.48 (t, J = 6.4 Hz, 2H), 2.41 (m, 1H), 2.29−2.11 (m, 3H), 1.85 (d, J = 1.8 Hz, 1H, OH), 1.70 (m, 2H), 1.59 (d, J = 1.5 Hz, 3H), 1.31−1.14 (m, 4H), 0.95 (d, J = 6.6 Hz, 3H), 0.87 (br t, J = 6.6 Hz, 3H), 0.83 (d, J = 6.6 Hz, 3H); ^{13}C NMR δ 138.6 (s), 135.9 (d), 133.3 (d), 133.0 (s), 132.3 (d), 128.3 (d, 2C), 127.6 (d, 2C), 127.5 (d), 81.8 (d), 72.9 (t), 69.7 (t), 41.3 (d), 39.8 (t), 31.8 (d), 29.5 (t), 29.3 (t), 20.9 (q), 20.6 (t), 17.3 (q), 14.2 (q), 10.9 (q); MS-EI *m*/*z* (relative intensity) 344 ($M^{+\bullet}$, 0.1), 273 (M − (*n*-Pr)$CHCH_3^+$, 0.1), 141 (27), 123 (23), 113 (46), 95 (86), 92 (19), 91 (100), 71 (41), 67 (12), 55 (11).

(4*E*,6*R*,7*R*,8*E*,10*R*)-7-[(*tert*-Butyldimethylsilyl)oxy]-6,8,-10-trimethyltrideca-4,8-dien-1-ol (53). To a solution of **51** (63 mg, 0.18 mmol) in CH_2Cl_2 (3 mL) at −78 °C were successively added 2,6-lutidine (80 μL, 0.69 mmol, 4 equiv) and *tert*-butyldimethylsilyl triflate (120 μL, 0.522 mmol, 3 equiv). After 3 h at −78 °C, the reaction mixture was poured into a saturated aqueous solution of $NaHCO_3$ and extracted with ether. The combined extracts were dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The crude silyl ether **52** was dissolved in THF/*t*-BuOH (6/1, 3.5 mL) and added to liquid ammonia (20 mL) at −78 °C. Finely cut lithium pieces (50 mg, 7.2 mmol, 39 equiv) were added all at once, and after 15 min at −78 °C, solid NH_4Cl (150 mg) was cautiously added to the reaction mixture. After evaporation of ammonia, water and ether were added. The resulting mixture was extracted with ether, and the combined extracts were washed with brine, dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by flash chromatography (petroleum ether/ether 80/20) to give 51 mg (75% from **51**) of **53** as a colorless oil: $[\alpha]^{20}_D$ −11.8 (*c* 1.0, $CHCl_3$); IR (film) 3280, 1250, 1055, 835, 775 cm^{-1}; ^1H NMR δ 5.46 (dd, J = 15.4 and 6.3 Hz, 1H), 5.38 (dt, J = 15.4 and 5.9 Hz, 1H), 4.99 (dm, J = 9.6 Hz, 1H), 3.66 (t, J = 6.6 Hz, 2H), 3.57 (d, J = 8.1 Hz, 1H), 2.37 (m, 1H), 2.22 (m, 1H), 2.12−2.00 (m, 2H), 1.64 (m, 2H), 1.54 (d, J = 1.5 Hz, 3H), 1.48 (br s, 1H, OH), 1.32−1.11 (m, 4H), 0.91 (d, J = 6.6 Hz, 3H), 0.89−0.84 (m, 3H), 0.86 (s, 9H), 0.80 (d, J = 7.0 Hz, 3H), −0.01 (s, 3H), −0.05 (s, 3H); ^{13}C NMR δ 134.7 (d + s, 2C), 134.1 (d), 128.6 (d), 83.8 (d), 62.7 (t), 40.8 (d), 39.9 (t), 32.5 (t), 31.7 (d), 29.1 (t), 25.9 (q, 3C), 20.8 (q), 20.7 (t), 18.2 (s), 17.1 (q), 14.2 (q), 11.2 (q), −4.5 (q), −4.9 (q); MS-EI *m*/*z* (relative intensity) 311 (M − *t*-Bu^+, 1), 256 (23), 255 (100), 185 (10), 171 (7), 127 (7), 75 (14), 73 (35).

(4*E*,6*R*,7*R*,8*E*,10*R*)-7-[(*tert*-Butyldimethylsilyl)oxy]-6,8,-10-trimethyltrideca-4,8-dienal (54). To a solution of **56** (47 mg, 0.13 mmol) in CH_2Cl_2 (4 mL) at 0 °C, were successively added pyridine (40 μL, 0.50 mmol, 4 equiv) and Dess−Martin periodinane (123 mg, 0.290 mmol, 2.3 equiv). After 4 h at rt, the reaction mixture was hydrolyzed with a 1.5 M aqueous solution of Na_2SO_3 (12 mL) and a saturated aqueous solution of $NaHCO_3$ (12 mL). After extraction with CH_2Cl_2, the combined extracts were washed with brine, dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The crude material was purified by flash chromatography (petroleum ether/Et_2O 92/8) to afford 40 mg (86%) of **54** as a colorless oil: $[\alpha]^{20}_D$ −11.8 (*c* 0.93, $CHCl_3$); IR (film) 1725, 1250, 1060, 870, 835, 775 cm^{-1}; ^1H NMR δ 9.78 (t, J = 1.8 Hz, 1H), 5.48 (dd, J = 15.4 and 7.2 Hz, 1H), 5.37 (dt, J = 15.4 and 5.9 Hz, 1H), 4.99 (dm, J = 9.6 Hz, 1H), 3.56 (d, J = 8.5 Hz, 1H), 2.50 (m, 2H), 2.44−2.31 (m, 3H), 2.22 (m, 1H), 1.53 (d, J = 1.5 Hz, 3H), 1.32−1.11 (m, 4H), 0.91 (d, J = 6.6 Hz, 3H), 0.89−0.82 (m, 3H), 0.86 (s, 9H), 0.79 (d, J = 6.6 Hz, 3H), −0.01 (s, 3H), −0.05 (s, 3H); ^{13}C NMR δ 202.3 (d), 135.6 (d), 134.7 (s), 134.3 (d), 126.8 (d), 83.7 (d), 43.5 (t), 40.8 (d), 39.9 (t), 31.7 (d), 25.8 (q, 3C), 25.3 (t), 20.7 (q+t, 2C), 18.2 (s), 17.0 (q), 14.2 (q), 11.1 (q), −4.5 (q), −5.0 (q); MS-CI$^+$ (CH_4) *m*/*z* (relative intensity) 367 (M + H^+, 10), 351 (20), 309 (14), 255 (55), 235 (100), 217 (15), 151 (22), 111 (21); HRMS (CI$^+$, CH_4) calcd for $C_{22}H_{43}O_2Si$ (M + H^+) 367.3032, found 367.3029.

Coupling of the C1−C12 and C13−25 Subunits. Methyl (2*S*)-2-((2*S*,5*S*,6*S*)-6-{(1*R*,2*R*,3*R*,5*S*,6*R*,9*E*,11*R*,12*R*,13*E*,-15*R*)-2,12-Bis[(*tert*-butyldimethylsilyl)oxy]-6-hydroxy-1,3,5,11,13,15-hexamethyl-4-oxooctadi-9,13-enyl}-5-methyltetrahydro-2*H*-pyran-2-yl)propanoate (56). To a solution of ethyl ketone **23** (60.0 mg, 0.136 mmol) in anhydrous CH_2Cl_2 (2.5 mL) at −78 °C was added a solution of freshly distilled $TiCl_4$ (190 μL, 0.75 M in CH_2Cl_2, 0.142 mmol, 1.05 equiv), and after 1 min, *i*-Pr_2NEt (30 μL, 0.17 mmol, 1.3 equiv) was added. After 1 h at −78 °C, a solution of aldehyde **54** (36 mg, 0.098 mmol, 0.72 equiv) in CH_2Cl_2 (2.5 mL) was added dropwise and the reaction was quenched 2 h later by addition of a saturated aqueous solution of NH_4Cl. The reaction mixture was diluted with Et_2O and H_2O, the layers were separated, and the aqueous phase was extracted with ether. The combined extracts were dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The ^1H NMR spectrum of the crude material indicated the formation of **60** with high diastereoselectivity (dr > 96/4). Purification by flash chromatography (petroleum ether/Et_2O 90/10, 85/15) afforded 55 mg (70%) of **56** as a colorless oil and 18 mg (30%) of ethyl ketone **23** was recovered: $[\alpha]^{20}_D$ −21.3 (*c* 1.15, $CHCl_3$); IR (film) 3440, 1740, 1695, 1255, 1165, 1060, 835, 775 cm^{-1}; ^1H NMR ($CDCl_3$) *d* 5.45 (dd, J = 15.4 and 6.2 Hz, 1H), 5.36 (m, 1H), 4.97 (br d, J = 8.5 Hz, 1H), 4.04 (m, 1H), 3.90 (dd, J = 7.0 and 3.3 Hz, 1H), 3.71 (s, 3H), 3.70 (m, 1H), 3.55 (d, J = 8.1 Hz, 1H), 3.42 (dd, J = 7.9 and 3.9 Hz, 1H), 3.13 (br s, 1H, OH), 3.03 (apparent quintet, J = 7.0 Hz, 1H), 2.67−2.57 (m, 2H), 2.36 (m, 1H), 2.23−2.11 (m, 3H), 1.99 (m, 1H), 1.87−1.70 (m, 2H), 1.65−1.39 (m, 4H), 1.53 (d, J = 1.5 Hz, 3H), 1.35−1.19 (m, 5H), 1.13 (d, J = 7.4 Hz, 3H), 1.08 (d, J = 7.0 Hz, 3H), 1.01 (d,

J = 6.6 Hz, 3H), 0.97 (d, J = 7.0 Hz, 3H), 0.93 (d, J = 7.0 Hz, 3H), 0.90 (d, J = 7.0 Hz, 3H), 0.87 (s, 9H), 0.88−0.84 (m, 3H), 0.85 (s, 9H), 0.78 (d, J = 7.0 Hz, 3H), 0.09 (s, 3H), 0.01 (s, 3H), −0.02 (s, 3H), −0.06 (s, 3H); ^{13}C RMN ($CDCl_3$) *d* 219.0 (s), 175.7 (s), 134.8 (s), 134.5 (d), 134.1 (d) 128.7 (d), 83.9 (d), 78.7 (d), 76.7 (d), 72.0 (d), 69.7 (d), 51.6 (q), 50.4 (d), 46.7 (d), 44.4 (d), 40.8 (d), 40.0 (d), 39.9 (t), 33.6 (t), 31.6 (d), 29.4 (t), 28.3 (d), 25.94 (q, 3C), 25.87 (q, 3C), 25.6 (t) 23.7 (t), 20.8 (q), 20.7 (t), 18.2 (q), 18.1 (s, 2C), 17.0 (q), 14.23 (q), 14.16 (q), 13.5 (q), 11.1 (q), 9.3 (q), 8.7 (q), −4.4 (q), −4.5 (q, 2C), −4.9 (q); HRMS (CI^+, NH_3) calcd $C_{46}H_{92}NO_7Si_2$ ($M + NH_4^+$) 826.6412, found 826.6417.

Methyl (2*S*)-2-[(2*S*,5*S*,6*S*)-6-((1*S*,2*S*,3*S*,4*S*,5*S*,6*R*,9*E*,-11*R*,12*R*,13*E*,15*R*)-2,4,6,12-Tetrahydroxy-1,3,5,11,13,15-hexamethyloctadi-9,13-enyl)-5-methyltetrahydro-2*H*-pyran-2-yl]propanoate (Zincophorin Methyl Ester) (2). To a solution of **56** (23 mg, 0.028 mmol) in MeOH (5 mL) at 0−5 °C was added portionwise $NaBH_4$ (40 mg, 0.11 mmol, 4 equiv) (four portions every 20 min). After 1 h, the reaction mixture was hydrolyzed with a saturated aqueous solution of Rochelle's salt and diluted with H_2O and Et_2O. The layers were separated, and the aqueous phase was extracted with Et_2O. The combined extracts were dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The crude intermediate diol **57** was dissolved in THF (5 mL) and to the resulting solution at 0−5 °C (polyethylene container), was added HF·Pyridine complex (1 mL). After 1.5 h at rt, the reaction mixture was diluted with Et_2O and H_2O, cautiously neutralized by addition of solid $NaHCO_3$, and extracted with Et_2O. The combined extracts were dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The crude material was purified by flash chromatography (*n*-hexane/EtOAc 50/50) to afford 11 mg (66%) of zincophorin methyl ester **2**: R_f 0.6 (*n*-hexane/EtOAc 50/50); R_f 0.4 (C_6H_6/Et_2O 50/50); $[\alpha]^{20}_D$ +21.3 (*c* 0.4, $CHCl_3$) (lit.[8] $[\alpha]_D$ +22.4 (*c* 0.89, $CHCl_3$), authentic sample: $[\alpha]_D$ +20.9 (*c* 2.0, $CHCl_3$)[1,6]); IR ($CHCl_3$) 3380, 1730, 1460, 1380, 1280, 1260, 1215, 1120, 1080, 1020, 970 cm^{-1}; ^{1}H NMR ($CDCl_3$) *d* 5.93 (s, 1H), 5.61 (dt, J = 15.1 and 6.6 Hz, 1H), 5.34 (dd, J = 15.1 and 8.8 Hz, 1H), 5.11 (br d, J = 9.2 Hz, 1H), 4.43 (d, J = 8.1 Hz, 1H), 4.12−4.06 (m, 3H), 3.76 (d, J = 10.3 Hz, 1H), 3.72 (s, 3H), 3.63 (dd, J = 8.8 and 1.8 Hz, 1H), 3.55 (d, J = 9.6 Hz, 1H), 3.44 (m, 1H), 3.23 (apparent dq, J = 10.8 and 7.0 Hz, 1H), 2.41 (m, 1H), 2.29−2.14 (m, 3H), 2.12 (br s, 1H), 2.08−1.96 (m, 2H), 1.78−1.52 (m, 4H), 1.60 (d, J = 1.5 Hz, 3H), 1.41−1.15 (m, 6H), 1.10 (d, J = 6.6 Hz, 3H), 1.08 (d, J = 6.6 Hz, 3H), 1.06 (d, J = 7.0 Hz, 3H), 0.94 (d, J = 6.6 Hz, 3H), 0.90−0.80 (m, 5H), 0.84 (d, J = 6.6 Hz, 3H), 0.82 (d, J = 6.2 Hz, 3H), 0.66 (d, J = 6.6 Hz, 3H); ^{13}C NMR ($CDCl_3$) *d* 175.6 (s), 135.7 (d), 133.4 (d), 133.3 (s), 133.2 (d), 84.4 (d), 84.0 (d), 81.8 (d), 76.1 (d), 74.5 (d), 68.9 (d), 52.3 (q), 41.8 (d), 39.9 (t), 39.7 (d), 38.4 (d), 37.5 (d), 34.4 (t), 34.0 (d), 31.8 (d), 31.6 (d), 29.1 (t), 26.3 (t), 25.0 (t), 21.0 (q), 20.6 (t), 17.7 (q), 17.5 (q), 14.8 (q), 14.2 (q), 13.3 (q), 11.25 (q), 11.20 (q), 10.8 (q); HRMS (CI^+, NH_3) calcd for $C_{34}H_{63}O_7$ ($M + H^+$) 583.4574, found 583.4578.

Zincophorin (1). To a solution of zincophorin methyl ester **2** (11 mg, 0.018 mmol) in THF/MeOH (2/1, 1.5 mL) was added a 2 M aqueous solution of LiOH (0.5 mL). After 1 h at 50 °C, the reaction mixture was acidified by addition of 35% aqueous hydrochloric acid (1 drop), diluted with deionized water (10 mL), and extracted with ether (4 × 15 mL). The combined extracts were dried over Na_2SO_4, filtered, and concentrated under reduced pressure. After purification by flash chromatography (hexane/ether: 60/40), an amorphous solid (11 mg), presumably an undetermined metal salt of zincophorin, was dissolved in ether and the resulting solution was washed with an aqueous solution of Na_2EDTA. The organic phase was dried over Na_2SO_4, filtered, and concentrated to afford 8 mg of zincophorin **1**, contaminated by traces of structurally unrelated impurities from organic solvents: ^{1}H NMR δ 5.49 (ddd, J = 15.1, 7.9, and 5.3 Hz, 1H), 5.36 (dd, J = 15.1 and 8.8 Hz, 1H), 5.11 (dd, J = 9.6 and 1.1 Hz, 1H), 4.07−4.00 (m, 2H), 3.74 (dd, J = 9.9 and 1.8 Hz, 1H), 3.69 (dd, J = 9.6 and 2.2 Hz, 1H), 3.57 (br d, J = 9.5 Hz, 1H), 3.47 (m, 1H), 3.27 (m, 1H), 2.46−2.10 (m, 4H), 2.08−1.96 (m, 2H), 1.82−1.57 (m, 4H), 1.59 (d apparent s, J = 1.1 Hz, 3H), 1.50 (m, 1H), 1.40−1.20 (m, 6H), 1.16 (d, J = 7.3 Hz, 3H), 1.13 (d, J = 7.0 Hz, 3H), 1.08 (d, J = 7.0 Hz, 3H), 0.93 (d, J = 6.6 Hz, 3H), 0.88 (m, 3H), 0.84 (d, J = 7.0 Hz, 3H), 0.78 (d, J = 6.6 Hz, 3H), 0.67 (d, J = 6.6 Hz, 3H) [structurally unrelated impurities: aromatic signals 7.4−7.8 ppm and paraffins: 1.25 (br s) and 0.86 (m)]; ^{13}C NMR δ 176.1 (s), 135.7 (d), 134.6 (d), 133.2 (s), 132.4 (d), 84.3 (d), 83.3 (d), 82.0 (d), 76.1 (d), 74.1 (d), 69.3 (d), 42.1 (d), 39.9 (t), 37.7 (d), 37.1 (d), 36.5 (d), 34.2 (t), 33.0 (d), 31.9 (d), 31.8 (d), 28.6 (t), 26.2 (t), 25.0 (t), 21.0 (q), 20.6 (t), 17.4 (q), 17.0 (q), 15.6 (q), 14.2 (q), 12.3 (q), 11.2 (q), 10.73 (q), 10.68 (q).

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Supporting Information Available: Tables of comparison of the NMR data of synthetic zincophorin methyl ester **2** and zincophorin **1** with those reported in the literature, and additional studies supporting the configurational assignment of ketones **45** and **46** and diol **57**. Copies of the NMR spectra of compounds **12a**,**c**, **14a-c**, **14′a**, **17**, **19**, **20**, **23**, **26**, **27**, **30**−**33**, **43**, **43′**, **44**, **46**, **50**, **51**, **53**, **54**, **56**, **2,** and **1**. This material is available free of charge via the Internet at http://pubs.acs.org.

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