A Synthetic Approach towards the C1 – C9 Subunit of Zincophorin

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The useful anti-infectious properties displayed by many naturally occurring polyoxygenated ionophores have been explained by their capacity to form lipophilic complexes with various cations, which affects proton – cation exchange processes across biological membranes.[1, 2]

In 1984, there were two independent reports on the isolation of apparently the same antibiotic from strains of *Streptomyces griseus*.[3, 4] On the basis of its exceptional high affinity for divalent cations and especially zinc, this antibiotic was given the trivial name zincophorin (Figure 1).[3–5] Zincophorin exhibits strong in vivo activity against Gram-positive bacteria[3, 4] and its methyl ester has also been reported to possess antiviral activity.[6]

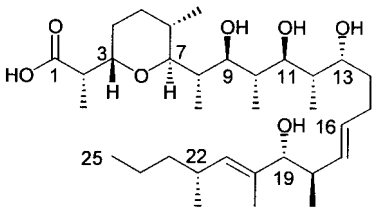
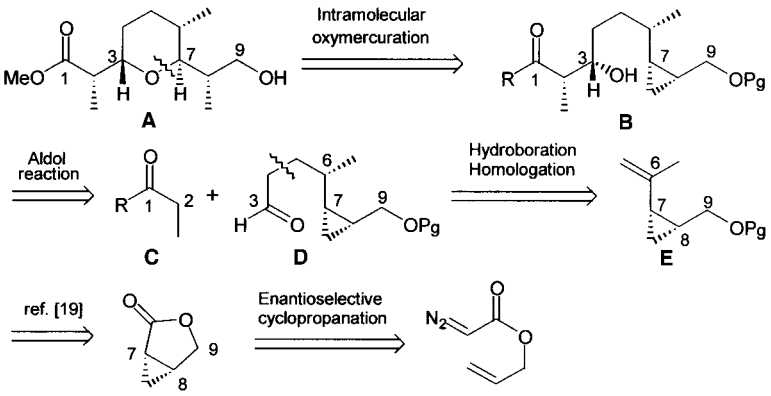


Figure 1. Structure of zincophorin.

The challenging structure of zincophorin has elicited considerable synthetic interest and syntheses of advanced elaborated fragments have been reported,[7–13] but to date a single total synthesis has been completed by the Danishefsky group.[7b] Herein, we report the results of our synthetic studies concerning a new approach towards the C1 – C9 subunit of zincophorin by using an intramolecular oxymercuration reaction of an appropriately substituted and enantiomerically enriched cyclopropylmethanol.

Whereas the intramolecular oxymercuration of alkenes has often been used to synthesize oxygenated heterocycles, and especially those encountered in naturally occurring ionophores,[14, 15] the corresponding reaction with cyclopropanes has received much less attention in the context of the total synthesis of natural products. As the intramolecular oxymercuration of cyclopropanes has been shown to proceed in some cases with high degrees of regio- and stereocontrol,[16, 17] a new approach towards the C1 – C9 subunit of zincophorin **A** was considered, to elaborate the trisubstituted tetrahydropyran (Scheme 1). This approach involved an intramolecular oxymercuration reaction, followed by reductive demercuration of the cyclopropylmethanol derivative **B**. According to the retrosynthetic analysis, the asymmetric carbon atoms C2 and C3 could be installed with the required absolute configurations by using a chiral-auxiliary-mediated aldol condensation between the enolate of ethylketone **C** and aldehyde **D**, which incorporates three contiguous stereocenters (C6 – C8). Based on previous studies,[18] the control of the relative configuration at the C6 atom could be achieved by performing a diastereoselective hydroboration of isopropenylcyclopropane **E**, followed by transformation to aldehyde **D**. Furthermore, the preparation of isopropenylcyclopropanes of type **E**, in an enantiomerically enriched form (*ee* value > 95 %) has been reported from 3-oxabicylo[3.1.0]hexan-2-one,[19] which is readily available by a rhodium-catalyzed enantioselective cyclopropanation of allyl diazoacetate (Scheme 1).[20]



Scheme 1. Retrosynthetic analysis for the C1 – C9 subunit of zincophorin. Pg = Protecting group.

The C1 – C9 subunit of zincophorin was synthesized (Scheme 2). Hydroboration of the isopropenylcyclopropane **1** with $BH_3 \cdot THF$, followed by a standard oxidative work-up with alkaline hydrogen peroxide, afforded, with a high diastereoselectivity (d.r. > 98/2), the corresponding alcohol **2** (91 %), with a methyl group *syn* to the adjacent cyclopropane.[18] In order to transform **2** to the aldehyde **5**, compound **2** was first oxidized with pyridinium chlorochromate (PCC) to the corresponding aldehyde,[21] and subsequent Horner – Wadsworth – Emmons olefination with triethyl phosphonoacetate afforded the α,β-unsaturated ester **3** (75 %). Compound **3** was then hydrogenated over platinum oxide in ethyl acetate to give the ethyl ester **4** (98 %), which was reduced with DIBAL-H (DIBAL-H = diisobutylaluminum hydride, toluene, −78 °C) to the aldehyde **5** (97 %).

The elaboration of a suitable precursor for the oxymercuration reaction required the installation of the C2 and C3 stereocenters with an *anti* relative configuration, by using a highly diastereoselective *anti*-aldol condensation between the *E*-boron enolate derived from the ethylketone **6**[22] and the aldehyde **5**, which afforded **7** in 83 % yield (d.r. > 96/4). With aldol **7** in hand, the feasibility of the intramolecular oxymercuration could then be tested, however treatment of **7** with mercuric trifluoroacetate in CH_2Cl_2 resulted in a number of products. As the *tert*-butyldiphenylsilyl group might interfere with this reaction,[23] it was removed by treatment of **7** with HF · pyridine to produce cyclopropylmethanol **8** (86 %). Indeed, when **8** was subjected to the oxymercuration

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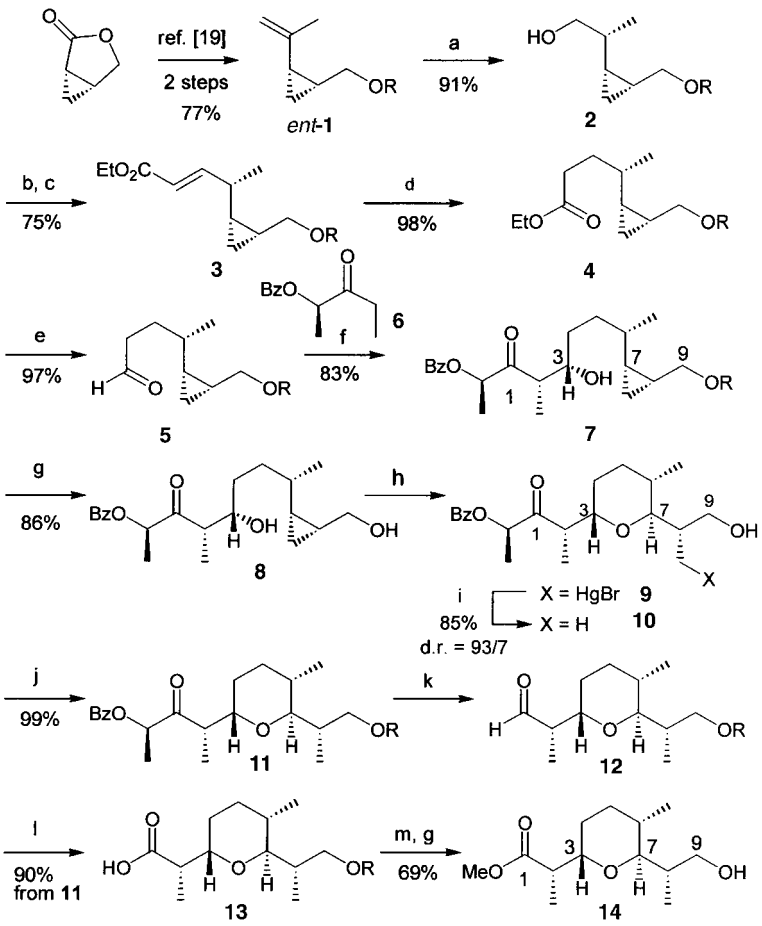

Scheme 2. Synthesis of the C1–C9 subunit of zincophorin. a) $BH_3 \cdot THF$/THF, $-30\,^{\circ}C \rightarrow$RT, then NaOH, H_2O_2; b) PCC, 4 Å molecular sieves, CH_2Cl_2, RT; c) NaH, $(EtO)_2P(O)$-CH_2-COOEt, THF; d) H_2, cat. PtO_2, EtOAc, RT; e) DIBAL-H, toluene, $-78\,^{\circ}C$; f) **6**, $EtNMe_2$, *c*Hex_2BCl, Et_2O, $0\,^{\circ}C$; add **5**, $-78\,^{\circ}C$, 2 h and $-23\,^{\circ}C$, 12 h, then MeOH, H_2O_2, pH 7 buffer; g) HF·pyridine, THF, RT; h) $Hg(OCOCF_3)_2$, CH_2Cl_2, RT then KBr/H_2O; i) *n*Bu_3SnH, toluene/THF, RT$\rightarrow 60\,^{\circ}C$ then CCl_4; j) *t*$BuPh_2SiCl$, imidazole, DMF, RT; k) $LiBH_4$, THF, $-20\,^{\circ}C \rightarrow$RT then $NaIO_4$, MeOH, RT; l) $NaClO_2$, NaH_2PO_4, 2-methylbut-2-ene, *t*BuOH/H_2O, RT; m) Me_3SiCHN_2, MeOH/C_6H_6. R = *t*$BuPh_2Si$, Bz = benzoyl.

procedure ($Hg(OCOCF_3)_2$, CH_2Cl_2, RT, aqueous KBr work-up), an extremely clean conversion to the organomercuric bromide **9** was observed. The latter was not purified but immediately subjected to reductive demercuration with tributyltin hydride;[24] this lead to tetrahydropyran **10** in 85% yield and with a high diastereoselectivity (d.r. = 93/7).[25] The relative configuration of **10** indicates that the intramolecular oxymercuration involved, as anticipated, an inversion of configuration at the C7 atom.[16, 17] The presence of the silyl protecting group interferes with the intramolecular oxymercuration of **7** (R = *t*$BuPh_2Si$), and implies additional deprotection and protection steps. The corresponding benzyl ether derivative was therefore synthesized (R = CH_2Ph), but its intramolecular oxymercuration, followed by reductive demercuration, proceeded in lower yield (46%) and diastereoselectivity (d.r. = 85/15) than for **8**. Therefore, the presence of the free alcohol at C9 was more appropriate for the intramolecular oxymercuration step, and the synthesis of the C1–C9 subunit of zincophorin was pursued from **10** (Scheme 2). The alcohol **10** was transformed to the *tert*-butyldiphenylsilyl ether **11** (99%), and reduction with lithium borohydride, followed by an oxidative cleavage with sodium periodate, afforded the aldehyde **12**,[22] which was oxidized to the corresponding acid **13** (90% from **11**). Subsequent esterification with trimethylsilyldiazomethane and deprotection of the silyl ether lead to **14** (**14** = **A**; 69%),[26] which is the C1–C9 subunit of zincophorin.

The C1–C9 subunit of zincophorin has been synthesized by an approach that involves three key steps: a diastereoselective hydroboration of an optically enriched isopropenyl-cyclopropane, an *anti*-aldol condensation, and a diastereoselective intramolecular oxymercuration of a cyclopropylmethanol.

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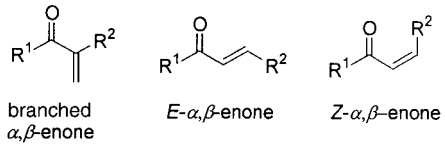
[25] Data for **10**: $[\alpha]_D^{20} = +44.0$ ($c = 0.04$, $CHCl_3$); IR (film): $\tilde{\nu}_{max} = 3440$, 1720, 1270, 1120, 720 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): $\delta = 8.08$ (m, 2H), 7.59 (m, 1H), 7.48 (m, 2H), 5.60 (q, $J = 6.9$ Hz, 1H), 4.09 (m, 1H), 3.52 (m, 2H), 3.36–3.24 (m, 2H), 2.28 (br s, 1H, OH), 1.89 (m, 1H), 1.67–1.60 (m, 3H), 1.55 (d, $J = 6.9$ 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 ppm (d, $J = 6.5$ Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 210.3$ (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 ppm (q); MS (CI^+, CH_4): *m/z* (%): 363 (100) $[M+H^+]$, 241 (20), 207 (22), 157 (92), 139 (61); HRMS (CI^+, CH_4): calcd for $C_{21}H_{31}O_5$ $[M+H^+]$: 363.2172, found: 363.2169. The relative configuration of compound **10** was confirmed by NMR spectroscopy, by differential NOE experiments performed on **11**.
[26] Data for **14**: $[\alpha]_D^{20} = +65.6$ ($c = 1.16$, $CHCl_3$); IR (film): $\tilde{\nu}_{max} = 3460$, 1740, 1720, 1460, 1435, 1380, 1275, 1255, 1170, 1040, 1020 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): $\delta = 3.92$ (ddd, $J = 11.0$, 5.5, and 1.5 Hz, 1H), 3.73 (s, 3H), 3.52 (dd, $J = 9.6$ and 2.6 Hz, 1H), 3.46 (m, 2H), 3.15 (dq, $J = 11.0$ and 7.0 Hz, 1H), 3.02 (br s, 1H, OH), 1.84 (m, 1H), 1.76–1.49 (m, 4H), 1.25 (m, 1H), 1.06 (d, $J = 6.6$ Hz, 3H), 0.82 (d, $J = 7.0$ Hz, 3H), 0.81 ppm (d, $J = 6.3$ Hz, 3H), ^{13}C NMR (75 MHz, $CDCl_3$): $\delta =$ 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 ppm (q); MS (EI): *m/z* (%): 244 (3) $[M^+]$, 185 (100), 157 (38), 153 (93), 139 (26), 126 (34), 125 (43), 121 (28), 99 (28), 97 (44), 95 (41), 88 (49), 82 (28), 81 (34), 69 (43), 59 (42), 55 (65); HRMS (CI^+, CH_4): calcd for $C_{13}H_{25}O_4$ $[M+H^+]$: 245.1753, found: 245.1750.

Efficient and Selective Hydroacylation of 1-Alkynes with Aldehydes by a Chelation-Assisted Catalytic System**

Chul-Ho Jun,* Hyuk Lee, Jun-Bae Hong, and Bong-Il Kwon

Intermolecular hydroacylation is one of the most efficient methods for preparing ketones from olefins and aldehydes.[1] Recently, we developed an efficient catalytic system for the intermolecular hydroacylation of 1-alkenes by using 2-aminopyridine derivatives as a chelating auxiliary.[2] Hydroacylation of alkynes with aldehydes is also very interesting in terms of regio- and stereoselective synthesis since three possible isomers of α,β-enones can be generated from this reaction: branched as well as linear *E*- and *Z*-α,β-enones (Scheme 1).

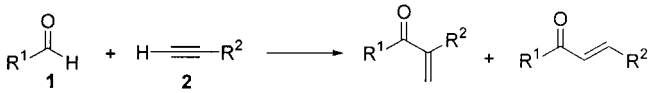


Scheme 1. Possible isomers of α,β-enones that can be generated from the hydroacylation of alkynes with aldehydes.

Although the intramolecular hydroacylation of alkynals was developed recently,[3] intermolecular hydroacylation of alkynes still remains little explored, and only a few nonselective examples have been reported with limited applications to internal alkynes[4] or benzaldehydes that bear a coordination site such as a hydroxy group at the *ortho* position.[5] Herein, we report a highly regio- and stereoselective intermolecular hydroacylation of terminal alkynes **2** with aldehydes **1** in the presence of a chelation-assisted catalytic system: $[Rh(PPh_3)_3Cl]$ (**3**), 2-amino-3-picoline (**4**), and benzoic acid (**5**). This is the most efficient catalytic system to date for the synthesis of branched or linear α,β-enones from 1-alkynes and aldehydes.

The reaction of benzaldehyde (**1a**) and 1-hexyne (**2a**) in the presence of the cocatalyst system consisting of **3** (5 mol%), **4** (40 mol%), and **5** (20 mol%) was performed in toluene at 80 °C for 12 h to afford the branched α,β-enone **6a** in 92% yield after chromatographic isolation (Table 1, entry 1). No direct selective synthetic methods for the preparation of branched α,β-enones have been reported previously, although syntheses of branched (1,1-disubstituted) vinyl compounds by hydrosilylation,[6] hydrophosphorylation,[7] and dimerization of 1-alkynes[8] have been reported. It was found that most aromatic aldehydes tested underwent smooth hydroacylation with primary alkyl alkynes to produce branched α,β-enones **6** exclusively in good to excellent yields (Table 1, entries 2–9).[9]

Table 1. Rh^I-catalyzed hydroacylation of various aldehydes and 1-alkynes.[a]



Entry	**1** (R^1)	**2** (R^2)[b]	**6**/**7**	Yield [%][c]
1	**a** (Ph)	**a** (n-C_4H_9)	100:0 (**6a**/**7a**)	92 (100)
2		**b** (n-C_6H_{13})	100:0 (**6b**/**7b**)	93 (98)
3		**c** ($PhCH_2$)	100:0 (**6c**/**7c**)	66 (71)
4	**b** (p-$CF_3C_6H_4$)	**a**	100:0 (**6d**/**7d**)	95 (100)
5	**c** (p-$MeOC_6H_4$)		100:0 (**6e**/**7e**)	76(85)
6	**d** (naphthyl)		100:0 (**6f**/**7f**)	83 (88)
7	**e** (3-thiophenyl)		100:0 (**6g**/**7g**)	96 (100)
8	**f** (4-pyridyl)		100:0 (**6h**/**7h**)	78 (100)
9	**g** (3-pyridyl)		100:0 (**6i**/**7i**)	79 (100)
10	**h** (2-pyridyl)			0
11	**i** (n-C_5H_{11})	**a**	78:22 (**6j**/**7j**)	85
12		**d** (t-C_4H_9)	0:100 (**6k**/**7k**)	74
13	**j** (cyclohexyl)	**a**	81:19 (**6l**/**7l**)	98 (100)[d]
14		**d**	0:100 (**6m**/**7m**)	63

[a] Reagents and conditions: $[Rh(PPh_3)_3Cl]$ (**3**; 5 mol%), 2-amino-3-picoline (**4**; 40 mol%), benzoic acid (**5**; 20 mol%), toluene, 80 °C, 12 h. [b] Two equivalents of **2** (based on the aldehyde) were used. [c] GC yields are given in parentheses, and <1% yields of side products were ignored. [d] Reaction time: 2 h.

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