Alkyne Metathesis

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Selective Formation of a Trisubstituted Alkene Motif by *trans*-Hydrostannation/Stille Coupling: Application to the Total Synthesis and Late-Stage Modification of 5,6-Dihydrocineromycin B**

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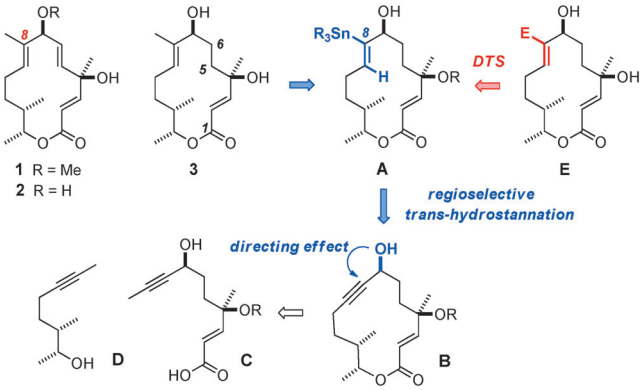
Abstract: *Countless natural products of polyketide origin have an E-configured 2-methyl-but-2-en-1-ol substructure. An unconventional entry into this important motif was developed as part of a concise total synthesis of 5,6-dihydrocineromycin B. The choice of this particular target was inspired by a recent study, which suggested that the cineromycin family of antibiotics might have overlooked lead qualities, although our biodata do not necessarily support this view. The new approach consists of a sequence of alkyne metathesis followed by a hydroxy-directed trans-hydrostannation and a largely unprecedented methyl-Stille coupling. The excellent yield and remarkable selectivity with which the signature trisubstituted alkene site of the target was procured is noteworthy considering the rather poor outcome of a classical ring-closing metathesis reaction. Moreover, the unorthodox ruthenium-catalyzed trans-hydrostannation is shown to be a versatile handle for diversity-oriented synthesis.*



Scheme 1. Structures of albocycline (**1**), cineromycin B (**2**), and 5,6-dihydrocinermycin B (**3**), together with a retrosynthetic disconnection of the latter. DTS = diverted total synthesis.

Albocycline (ingramycin, **1**)[1,2] and cineromycin B (**2**)[3] are the parent compounds of a class of antibiotics which consist of bare 14-membered macrolactone rings devoid of any appended sugar residues (Scheme 1).[4] Although the biological spectrum of these macrolides was judged (too) narrow, a recent report calls for a re-evaluation.[5] Specifically, **1** was reported to inhibit the growth of methicillin-resistant *Staphyllococcus aureus* (MRSA) with a potency similar to that of vancomycin, the drug of last resort.[6–8] This finding insinuates that the cineromycins might be overlooked lead structures in the quest for anti-infective agents against resistant bacterial strains of utmost clinically significance.

More detailed investigations, including a broader screening campaign, will be necessary to validate this aspect. Since **1** and **2** are fairly labile, an important issue to be addressed concerns the stability of the scaffold. To this end, the naturally occurring but rare sister compound 5,6-dihydrocineromycin B (**3**)[9] was deemed a sensible starting point, as it lacks the doubly allylic environment about the C7-OR substituent and is, therefore, expected to be chemically more robust. Like the parent macrolides themselves,[10,11] **3** had already been targeted by total synthesis in the past, but no relevant biodata were disclosed.[12–14] Therefore, a fresh approach was planned with the intention to secure a good material supply, resolve some previously unmet selectivity issues, and enable late-stage modifications by diverted total synthesis (DTS) for biological testing.[15]

These objectives were met by an unconventional approach to the trisubstituted $\Delta^{8,9}$-alkene subunit of **3** (Scheme 1). Ring-closing olefin metathesis (RCM) had previously been used to forge the macrocycle at this particular site, but was found inefficient (40%) despite the high loading of the second-generation Grubbs catalyst and the forcing conditions (25 mol%, 48 h, refluxing CH_2Cl_2).[14,16,17] We conjectured that ring-closing alkyne metathesis (RCAM)[18,19] might provide a more favorable and predictable solution, as long as the resulting cycloalkyne **B** could be elaborated into a methyl-branched *E*-alkene. The ruthenium-catalyzed *trans*-hydrostannation recently described by our group was thought to pave the way.[20,21] This reaction is distinguished by an unorthodox stereochemical course and shows excellent levels of regioselectivity when applied to unprotected propargyl alcohol derivatives. By virtue of a massive directing effect exerted by the protic site, the R_3Sn group is delivered to the proximal C atom of the alkyne unit with high fidelity. This pattern should bring an α-alkenylstannane of type **A** into reach, which might then be

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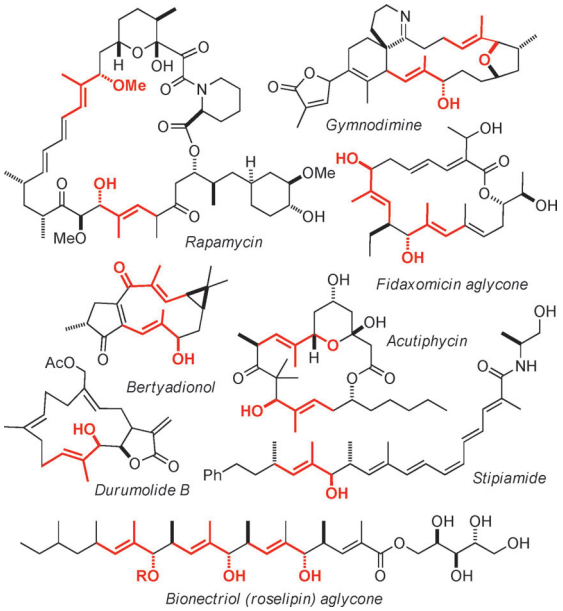
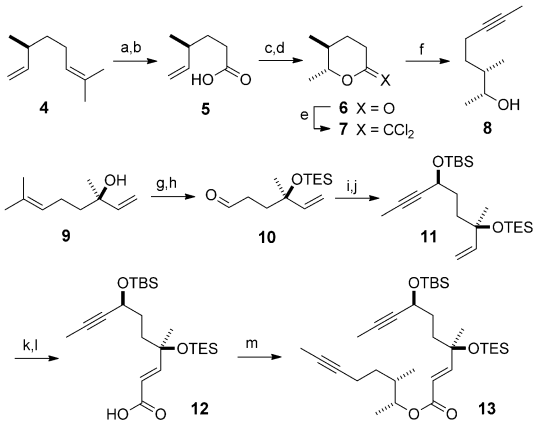
elaborated to the targeted natural product **3** by Stille coupling.[22] At the same time, the interim trialkyltin residue provides a handle for late-stage modifications other than methylation (**A**→**E**); in the present context, it might allow the first structure/activity relationships to be probed with little extra synthetic effort. In any case, the proposed strategy is expected to be of more general interest, since *E*-configured 2-methyl-but-2-en-1-ol motifs feature prominently in countless natural products of polyketide origin (Scheme 2).



Scheme 2. Small selection of structurally diverse natural products comprising one or more *E*-configured 2-methyl-but-2-en-1-ol subunits (or immediate derivatives thereof).

(*S*)-Citronellene (**4**) served as the entry point for the preparation of the necessary alcohol building block (Scheme 3). Selective ozonolysis of the more highly substituted double bond followed by oxidation of the resulting aldehyde furnished multigram amounts of acid **5**, which was iodo-lactonized with iodine in MeCN at ambient temperature.[23,24] Reduction of the C–I bond preceded the conversion of the resulting lactone **6** into the required non-terminal alkyne according to a procedure recently described by our group.[25,26] To this end, **6** was treated with CCl_4/PPh_3 and the resulting dichloro-olefin **7** treated with MeLi in the presence of a catalytic amount of $[Cu(acac)_2]$ to cause a reductive alkylation with direct formation of the methyl-capped acetylene derivative **8**.

A practical synthesis of the acid segment started from inexpensive (*R*)-linalool (**9**; Scheme 3). Protection with a TES group followed by a selective ozonolysis gave aldehyde **10**,[27] which was subjected to a Carreira reaction to set the missing stereocenter while installing the alkyne handle for the envisaged macrocyclization.[28] Although the use of propyne has little precedent,[29] the addition worked well on a multigram scale. In this context, we recall that two of the three reported syntheses of **3** failed to achieve any selectivity while

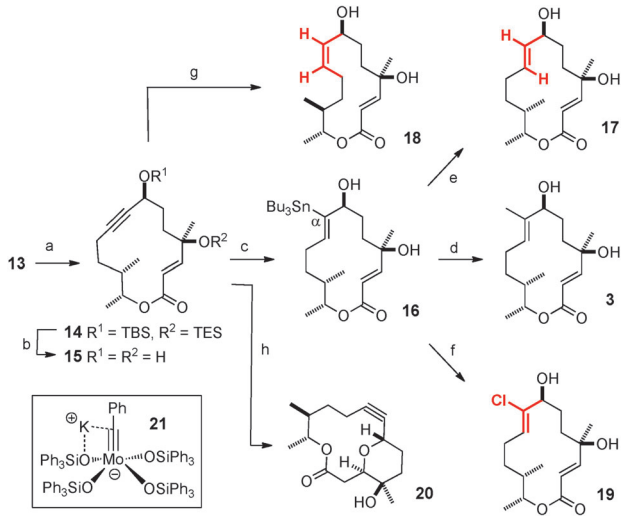


Scheme 3. Reagents and conditions (the scales refer to the single largest batches): a) O_3, CH_2Cl_2, −78 °C, then Me_2S, RT; b) NaOCl, H_2O_2, NaH_2PO_4, *t*BuOH/H_2O (2:1), 80% (over both steps, 15 g scale); c) I_2, MeCN, 73% (3.2 g scale); d) Bu_3SnH, benzene, reflux, 88% (3.7 g scale); e) CCl_4, PPh_3, THF, reflux; f) MeLi, $[Cu(acac)_2]$ (10 mol%), Et_2O, 0 °C, 74% (over both steps, 1.1 g scale); g) TESCl, imidazole, DMAP (5 mol%), CH_2Cl_2, 99%, (5.9 g scale); h) O_3, CH_2Cl_2, pyridine, −78 °C, then Me_2S, RT, 77%, (5.8 g scale); i) propyne, Zn-$(OTf)_2$, (−)-*N*-methylephedrine, Et_3N, toluene, RT, then **10**, 94% (3.9 g scale, d.r. > 20:1); j) TBSCl, imidazole, CH_2Cl_2, quant. (4.2 g scale), k) O_3, CH_2Cl_2, −78 °C, then Me_2S, RT, 67% (5.6 g scale); l) $(EtO)_2P(O)CH_2COOH$, TMEDA, DBU, $Zn(OTf)_2$, THF, 0 °C→RT, 80% (3.3 g scale); m) **8**, DCC, DMAP, CH_2Cl_2, 0 °C, 84% (2 g scale). acac = acetylacetonato, DBU = 1,8-diazabicyclo[5.4.0]undec-7-ene, DCC = dicyclohexylcarbodiimide, DMAP = 4-dimethylaminopyridine, TBS = *tert*-butyldimethylsilyl, TES = triethylsilyl, Tf = trifluoromethanesulfonyl, TMEDA = *N*,*N*,*N*′,*N*′-tetramethylethylenediamine.

setting the critical stereocenter at C7;[12,13] the excellent outcome of the asymmetric propynylation (d.r. > 20:1) therefore constitutes a notable distinction. The resulting product **11** was readily elaborated into the acid segment **12**; of the necessary operations, the zinc-promoted variant of the Horner–Wadsworth—Emmons olefination is probably most noteworthy as it delivers an unprotected carboxylic acid right away.[30] Esterification with alcohol **8** then furnished diyne **13** in readiness for ring closure.

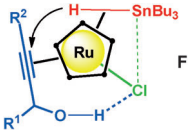
This critical step was accomplished by the molybdenum alkylidyne ate complex **21** endowed with triphenylsilanolate ligands which is arguably one of the most active and selective alkyne metathesis catalysts known to date (Scheme 4).[31,32] The reaction proceeded smoothly at ambient temperature to afford the corresponding 14-membered cycloalkyne **14** in excellent yield; this outcome is fully appreciated when compared with the difficulties encountered in closing the ring by RCM at the same site (see above).[14] Next, the silyl protecting groups were cleaved with HF·pyridine and the resulting diol **15** treated with Bu_3SnH in the presence of $[Cp^*RuCl_2]_n$ (5 mol%)[33] to give the expected α-alkenylstannane **16**, basically as a single isomer (α/β > 20:1, *E*/*Z* > 20:1). It is also important to note that the transannular alkene, which competes with the alkyne for coordination to the π-affine ruthenium catalyst, did not interfere with the directed *trans*-hydrostannation.

The gratifying outcome of this operationally simple but exquisitely selective transformation is confidently ascribed to



Scheme 4. Reagents and conditions (the scales refer to the single largest batches): a) **14** (10 mol%), MS 5 Å, toluene, 92% (800 mg scale), b) HF·pyridine, THF, pyridine, 84% (545 mg scale); c) Bu_3SnH, $[Cp^*RuCl_2]_n$ (5 mol%), CH_2Cl_2, 83% (336 mg scale); d) $[Pd(PPh_3)_4]$ (5 mol%), $[Ph_2PO_2][NBu_4]$, CuTC, MeI, DMF, 92% (286 mg scale), see text; e) CuTC, $[Ph_2PO_2][NBu_4]$, DMF, 78% (15 mg scale); f) $CuCl_2$, THF, 77% (42 mg scale); g) H_2 (1 atm), $Pd/BaSO_4$, THF, pyridine, 74% (20 mg scale); h) TBAF, THF, 97% (130 mg scale). Cp* = pentamethylcyclopentadienyl, CuTC = copper thiophene-2-carboxylate, TBAF = tetra-*n*-butylammonium fluoride.

the cooperativity between the propargylic -OH group in the substrate and the {Ru-Cl} unit of the catalyst.[34] Structural as well as spectroscopic data suggest that the chloride ligand engages in hydrogen bonding, which aligns and locks the alkyne within the coordination sphere of the catalyst. At the same time, the incoming stannane reagent is predisposed in a matching orientation by an additional interligand interaction between the {Ru-Cl} group and the tin center; the resulting favorable array of type **F** is thought to warrant the excellent regioselectivity of the ensuing *trans*-addition.[34]



F

Although the conversion of **16** into **3** by a Stille reaction with MeI (or an equivalent thereof) seemed straightforward, we were surprised to find hardly any precedent.[35,36] Instead, indirect solutions prevail in the literature, in which an alkenylstannane is first converted into the corresponding iodide, which is then treated with a stoichiometric amount of Me_2CuLi[37] or cross-coupled with an appropriate methyl donor.[38] Alternatively, transmetalation strategies were exercised that rely on the initial transformation of the alkenyltin species into a more reactive organolithium or organocopper reagent which is then trapped with MeX.[39] In the present case, however, an organolithium intermediate is excluded by the presence of the lactone group in **16**, whereas a Sn→Cu exchange mandates an excess of a cuprate reagent that might endanger the Michael acceptor site of this elaborate substrate. Gratifyingly though, such maneuvering was found to be unnecessary: after some optimization, we were able to adapt a procedure previously described by our group for demanding Stille coupling reactions to the current needs.[40–42] Specifically, the rapid sequential addition of CuTC (1.05 equiv)[43] and MeI (1.5 equiv) to a stirred solution of **16**, $[Pd(PPh_3)_4]$ (5 mol%), and $[Ph_2PO_2][NBu_4]$ (1.1 equiv)[44] in DMF at ambient temperature gave 5,6-dihydrocineromycin (**3**) in excellent yield. The present synthesis is shorter and considerably more selective than any the previous ones; the data of synthetic **3** thus formed are in accord with the literature data.[9,12,13,45]

The order of addition as well as the stoichiometry of the reactants is important in the methyl-Stille reaction to ensure full conversion but avoid competing protodestannation. While this bias mandated careful optimization, it also provided an unexpected opportunity. Thus, treatment of **16** with stoichiometric amounts of CuTC and $[Ph_2PO_2][NBu_4]$ in DMF followed by an aqueous work up furnished the corresponding des-methyl derivative **17** as a first non-natural analogue for screening purposes. This mild and essentially neutral procedure compares favorably to other methods for protodestannation, which usually employ a strong Brønsted acid or a harsh nucleophilic additive (MeONa, CsF) and are therefore limited in terms of their functional-group tolerance.[46] The *Z*-configured counterpart **18** was also within reach by a routine Lindlar hydrogenation of the alkyne precursor **15**. As a further testimony of the flexibility of the chosen approach, the tin residue was exchanged for a chloride substituent upon treatment of **16** with $CuCl_2$;[47] NOE contacts confirm that this transformation proceeded with retention of the double-bond configuration to give **19** as the only product in good chemical yield. Finally, a more profound structural modification was procured on treatment of **14** with TBAF; by virtue of the basic character of this reagent, the incipient diol **15** engages in a transannular oxa-Michael reaction to give the bicyclic product **20**. Its constitution was confirmed by single-crystal X-ray diffraction.[48] Figure 1 shows this unusual

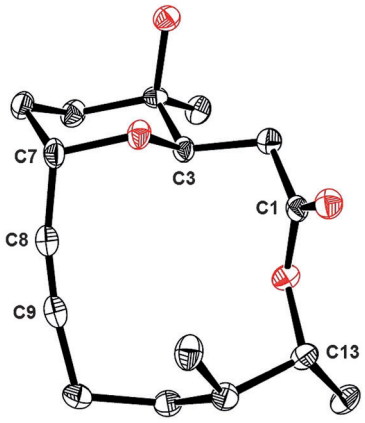


Figure 1. Structure of compound **20** in the solid state; cineromycin numbering scheme.

scaffold incorporating a 1,5-*trans*-disubstituted pyrane ring, which forces the C8–C9 triple bond to bend away from linearity (C7-C8-C9 167.4°).

These analogues comprise deep-seated structural point mutations, none of which could be instigated by derivatization

of the natural product itself.[15] To our dismay, however, neither **3** nor any of the synthetic descendants described above showed appreciable activity against a panel of ten different bacteria (including *S. aureus*) and one fungus.[49] These data suggest that the chemically vulnerable doubly allylic alcohol substructure in the top region of the purportedly highly potent antibiotic albocycline (**1**)[5] is not a particularly permissive site. Although these findings cast some doubt on the potential lead qualities of this macrolide, further analogues need to be tested for a more informed conclusion.

This biological connotation notwithstanding, the present study outlines an effective way of grafting stereodefined trisubstituted olefins (and related motifs) flanked by a hydroxy group, a structural pattern that is present in numerous natural products. The chosen approach is based on the regio- and stereoselective functionalization of an internal alkyne, comprises only transformations of proven functional-group tolerance, and therefore qualifies for late-stage applications; it also represents the first implementation of a directed *trans*-hydrostannation into target-oriented synthesis. At the same time, the scope of the venerable Stille–Migita coupling was expanded to encompass MeI as an electrophilic partner. Further studies on this and related chemistry will be reported shortly.

Keywords: alkyne metathesis · cross-coupling · hydrostannation · natural products · ruthenium

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[48] CCDC 1048778 (**20**) contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

[49] In a liquid culture dilution assay, the minimum inhibition concentration (MIC) of **3** against *S. aureus* Newman was 16 $\mu g\,mL^{-1}$, whereas the MIC of **3**, **15**, **17**, **18**, **19**, and **20** was invariably $\geq 64\ \mu g\,mL^{-1}$ against all other tested bacterial and fungal strains.

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Communications

Alkyne Metathesis

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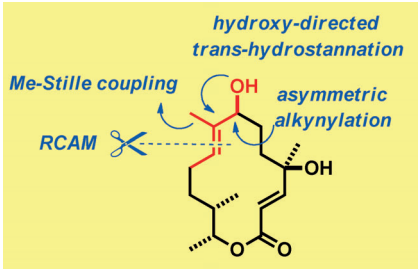
Selective Formation of a Trisubstituted Alkene Motif by *trans*-Hydrostannation/Stille Coupling: Application to the Total Synthesis and Late-Stage Modification of 5,6-Dihydrocineromycin B



Directed although indirect: The antibiotic dihydrocineromyin B is one of countless natural products featuring an *E*-configured 2-methyl-but-2-en-1-ol substructure (see picture, RCAM = ring-closing alkyne metathesis). The key step in the synthesis was a ruthenium-catalyzed hydroxy-directed *trans*-hydrostannation of an alkyne. The method is efficient, broadly applicable, and suited to late-stage diversification.