< 50 % yield at − 20 °C, whereas Yb[Otf]$_3$ provided **23** in 72 % yield at room temperature.
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[13] Compound **27** was previously described by Nicolaou et al.[2b] The spectral data obtained for **27** here ($[\alpha]_D^{23} = +5.0$ ($c = 0.26$, $CHCl_3$), IR, ^{1}H and ^{13}C NMR, HRMS) are fully consistent with those reported in reference [2b].
[14] For the assignment of methylene protons, the higher field proton was suffixed by a (e.g., H_a), while the lower field proton was suffixed by b (e.g., H_b).

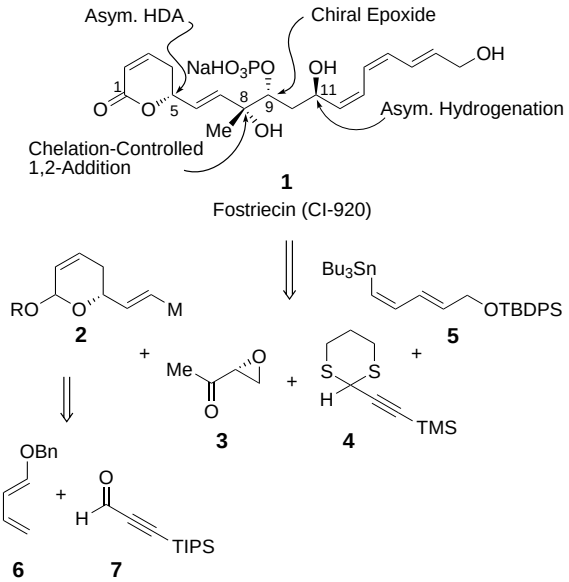
Total Synthesis of Fostriecin (CI-920)**

David E. Chavez and Eric N. Jacobsen*

Fostriecin (CI-920, **1**; see Scheme 1) is a structurally interesting antitumor agent that was first isolated in 1983 by scientists at Warner Lambert-Parke Davis.[1] It displays in vitro activity against a broad range of cancerous cell lines as well as in vivo antitumor activity,[2] and it appears to operate by a novel mechanism involving inhibition of the mitotic entry checkpoint.[3] In this context, fostriecin is a potent inhibitor of protein serine/threonine phosphatases, and it is in fact the most selective protein phosphatase inhibitor identified to date (10^4 times greater affinity for the protein phosphatases PP2A and PP4 versus PP1).[4]

It was not until 1997 that a correct and complete stereochemical assignment of fostriecin was made by Boger and coworkers,[5] and that was followed very recently by a report of the first total synthesis from the same group.[6] Certainly, the development of a practical synthetic route to fostriecin is warranted based on its interesting biological properties. In addition, clinical trials carried out at the National Cancer Institute were halted early in Phase I over concerns about the stability and purity of the natural material.[7] A flexible synthetic route to **1** could serve as a basis for the discovery of analogues with similar biological but more desirable physical properties. In addition, the structure of fostriecin poses an assortment of interesting challenges to an efficient synthetic design, including the presence of the unsaturated lactone,[8] the C8 – C11 triol monophosphate component, and the conjugated *Z*,*Z*,*E*-trienol unit. Herein we report a new total synthesis of fostriecin. Our approach integrates highly effective asymmetric catalytic reactions to generate key chiral building blocks, and efficient coupling reactions to enable their convergent assembly.

The synthetic plan involves assembly of four fragments (**2** – **5**) of similar complexity (Scheme 1). Epoxyketone **3** plays a central role in our strategy, serving not only as the source of the C9 stereocenter, but also as a lynchpin for joining the left-hand vinyl lactone unit **2** and the right-hand triene diol fragment. We anticipated applying the [(salen)Co]-catalyzed hydrolytic kinetic resolution (HKR) reaction to the preparation of enantioenriched **3**, encouraged by the remarkable generality displayed by this method for the preparation of highly enantioenriched terminal epoxides.[9] However, while racemic **3** was prepared easily from inexpensive methyl vinyl ketone,[10] its HKR proved particularly challenging. Under standard conditions ((*S*,*S*)-**8**, 0.2 – 2 mol %, 0.55 equiv H_2O), precipitation of catalyst as the reduced [(salen)Co^{II}] complex was observed with low substrate conversion.[11] Fortunately, this problem proved relatively easy to circumvent. When the reaction was carried out under an atmosphere of O_2 instead of N_2 or air, reduction of catalyst was avoided and the HKR proceeded to completion affording **3** in > 99 % *ee* and 40 % yield (Scheme 2; possible yield = 50 %).



Scheme 1. Retrosynthetic analysis of **1**. TBDPS = *tert*-butyldimethylsilyl; TIPS = triisopropylsilyl

With an effective route to (*R*)-**3** in hand, the next key consideration in the synthesis was the diastereoselective addition of a vinyl organometallic such as **2** to the carbonyl group of **3** to assemble the two left-hand fragments and set the C8 tertiary alcohol stereocenter. While addition of Grignard reagents to **3** proceeded in THF with exclusive reaction at the ketone functionality, only modest diastereoselectivity (ca. 4:1)

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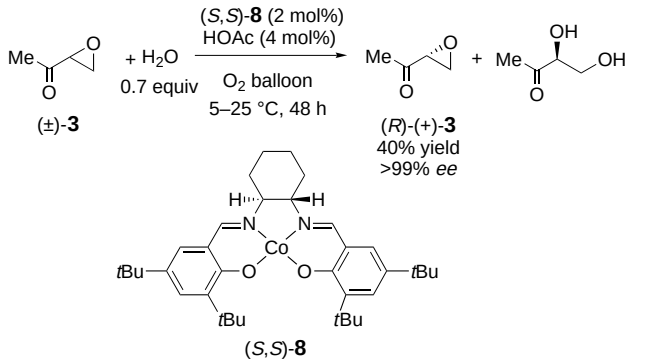
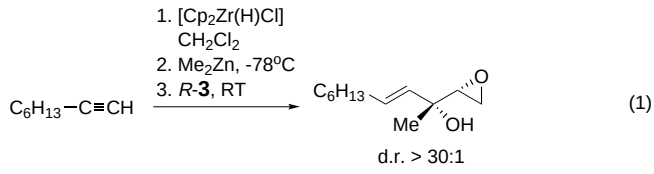


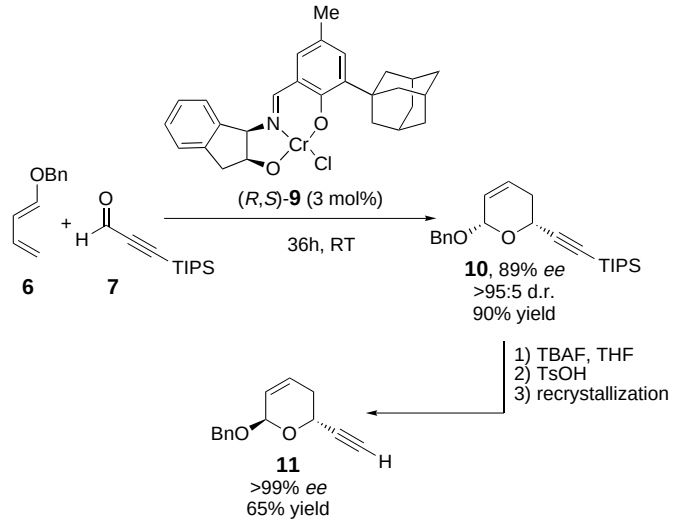
Scheme 2. Hydrolytic kinetic resolution of epoxyketone **3**.

was observed with the desired chelation control product predominating. A variety of alternative methods for addition of vinylorganometallic reagents to **3** was investigated, and the protocol developed by Wipf and co-workers[12] for the addition of vinyl zinc intermediates to aldehydes proved most effective. For example, hydrozirconation of model substrate 1-octyne, transmetalation with dimethylzinc and addition to **3** led to the isolation of the desired 1,2-addition adduct in good yield (75%) and with excellent diastereoselectivity (>30:1); the chelation control product was favored [Eq. (1)]. This represents the first extension of the Wipf methodology to ketone vinylation.



(1)

Having established a plausible strategy for coupling of fragments **2** and **3**, we sought an efficient enantioselective method for the preparation of alkynyl lactone **10** (Scheme 3).



Scheme 3. Preparation of **11** by means of the asymmetric hetero-Diels–Alder reaction catalyzed by **9**.

We were particularly intrigued by the possibility of applying the recently developed Cr-catalyzed hetero-Diels–Alder (HDA) reaction to this task, having established in earlier studies that cycloadditions between 1-methoxybutadiene and simple aldehydes are catalyzed by complex **9** with high enantioselectivity.[13] In the ideal case, it would be possible to establish the entire carbon framework of the left-hand fragment **2** in the HDA reaction, and with that in mind we investigated the reaction of alkoxybutadiene derivatives with ynal **7**. We were pleased to find that **7** was indeed an effective partner in the asymmetric HDA reaction, affording cycloadducts in good yield, diastereoselectivity and enantioselectivity (Scheme 3). Whereas a variety of 1-alkoxybutadiene derivatives underwent reaction with >95% *de* and >85% *ee*, benzyloxy derivative **6** led to product with highest yield. Desilylation of **10** with tetrabutylammonium fluoride (TBAF), followed by acidic workup, was accompanied by epimerization of the acetal to the more stable α-anomer **11a**. This intermediate underwent recrystallization to enantiomeric purity in good overall yield.

With the two left-hand chiral building blocks now readily accessible in >99% *ee*, we investigated their coupling using the Wipf procedure described above. Under carefully optimized conditions,[14] hydrozirconation/transmetalation of **11b** was followed by reaction with **3** to afford the desired addition product **12a** with excellent diastereoselectivity (>30:1; Scheme 4). Although the yield for this novel vinylation reaction was modest, this coupling enabled introduction of the C8 stereocenter with high selectivity at an early stage in the synthesis and provided advanced intermediate **12a** in only seven steps (five in the longest linear sequence) from commercially available materials.

The tertiary alcohol was protected to give silyl ether **12b**, and epoxide ring opening with the anion derived from dithiane **4**[15] proceeded in excellent yield to accomplish the second fragment coupling. Acetal hydrolysis followed by selective oxidation of the resulting lactol in the presence of the free secondary C9 alcohol provided **13**. Dithiane removal using Stork's protocol,[16] followed by protection of the secondary alcohol as PMB ether[17] **14** afforded the C8–C9 diol unit in orthogonally protected form, in anticipation of a later stage selective phosphorylation of the C9 alcohol.

The final stereocenter (C11) was established by using Noyori's transfer hydrogenation methodology.[18] The catalytic asymmetric reduction allowed us to control the relative stereochemistry of the 1,3-diol unit simply by selection of the appropriate enantiomer of the catalyst.[19] The reaction proceeded with high selectivity to provide **15** (d.r. >25:1).[20] Protection of the propargylic alcohol as a silyl ether, one-pot acetylene deprotection and iodination,[21] followed by PMB deprotection and *cis*-vinyl-iodide formation using a highly selective diimide reduction[22] provided vinyl iodide **16** (Scheme 4).

The final fragment coupling joined vinyl iodide **16** and the *Z*,*E*-stannane **5** (Scheme 5).[23] The cross-coupling was effected under ligand-free Stille coupling conditions[24] and proceeded with complete retention of olefin stereochemistry. Phosphorylation of the C9 alcohol of **17** was accomplished by using a modification of the protocol developed by Evans.[25]

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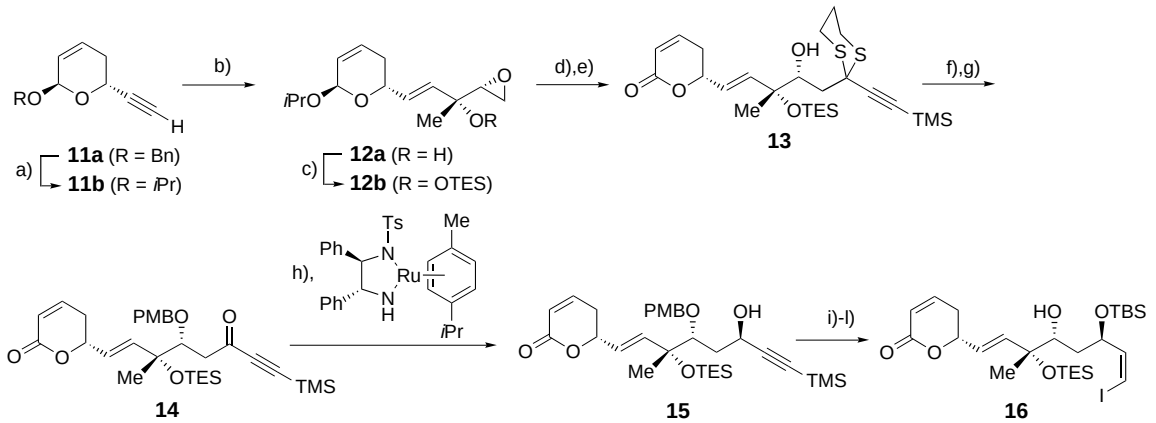
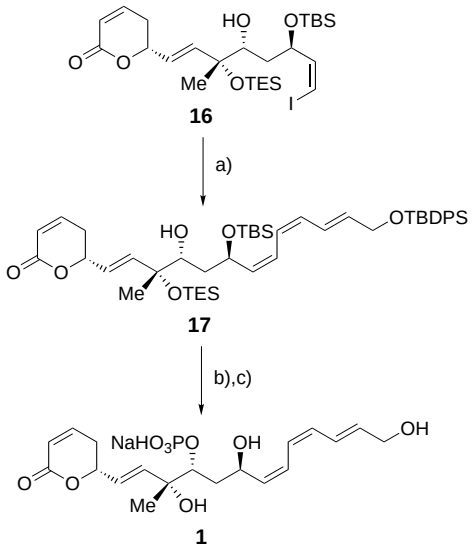


Scheme 4. Synthesis of the C_1-C_{13} fragment. a) TsOH, *i*PrOH, 90%; b) $[Cp_2Zr(H)Cl]$, CH_2Cl_2; then Me_2Zn, $-78\,^{\circ}C$, 10 min; then **3**, 4 h, RT; c) TESCl, imidazole, DMF; 45%, 2 steps; d) *n*BuLi, **4**, THF, $-40\,^{\circ}C$; then **12b**; 89%; e) PPTS, acetone/H_2O (4:1); then MnO_2, CH_2Cl_2; 65%, 2 steps; f) bis(trifluoroacetoxyiodobenzene), MeOH/H_2O (9:1); 70%; g) 4-MeO-benzyl trichloroimidate, $Ph_3C^+\,BF_4^-$, Et_2O; 83%; h) *i*PrOH; 36 h; 93%, >95:5 dr; i) TBSOTf, 2,6-lutidine, CH_2Cl_2; 80%; j) $AgNO_3$, NIS, acetone; 95%; k) DDQ, CH_2Cl_2; 100%; l) NBSH, THF/*i*PrOH (1:1), TEA; 85%; TES = triethylsilyl; TESCl = chlorotriethylsilane; TsOH = *p*-toluenesulfonic acid; PPTS = pyridinium *p*-toluenesulfonate; PMB = *p*-methoxybenzyl; TBSOTf = *tert*-butyldimethylsilyltrifluoromethanesulfonate; NIS = *N*-iodosuccinimide, DDQ = dichlorodicyanoquinone, NBSH = *o*-nitrobenzenesulfonylhydrazide; TEA = triethylamine; PMBOH = *p*-methoxybenzyl alcohol.



Scheme 5. Completion of the synthesis of fostriecin. a) $[PdCl_2(CH_3CN)_2]$, **5**, DMF; 85%; b) PCl_3, pyr; then PMBOH; then *t*BuOOH, CH_2Cl_2; 65%; c) HF, CH_3CN; then pyr; 45%.

Global deprotection of the silyl and *p*-methoxybenzyl groups afforded **1**, with spectroscopic and chromatographic properties identical to those of natural fostriecin .

The synthesis of fostriecin was thus completed in 17 steps in the longest linear sequence. Our approach made use of asymmetric catalytic reactions to obtain building blocks **11** and **3** in >99% *ee*. Epoxyketone **3** is now readily accessible using HKR methodology, and holds promise as a versatile chiral building block for asymmetric synthesis. In the context of the fostriecin synthesis, the use of **3** allowed rapid access to advanced intermediate **13** through selective ketone alkylation and subsequent epoxide ring opening. Overall, control of three of the four stereocenters of fostriecin was exerted by means of asymmetric catalytic reactions, while the tertiary C8 allylic alcohol center was installed by using a novel, highly diastereoselective alkenylation of epoxyketone **3**. This synthesis further illustrates the power of the chiral building block strategy for natural product synthesis, and provides easy access to structural analogues of fostriecin for further study.

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A Practical and Green Chemical Process: Fluoroalkyldistannoxane-Catalyzed Biphasic Transesterification

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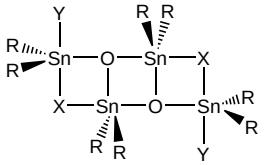
Transesterification is one of the most important reactions in organic synthesis.[1] Besides its utility in the laboratory, this reaction is significant in various industrial processes, such as the production of fatty acids, paints, polyesters, etc. Hence it is important that the reaction be practical and green. In its long history, numerous methods have been advanced, but few are satisfactory in view of process chemistry. The difficulty stems primarily from the equilibration of the reaction. Two strategies are invoked to bias the equilibrium in favor of the product: use of one of the reactants (RCOOR′ or R″OH) in excess or continuous removal of the alcohol formed (R′OH) [Eq. (1)]. The former treatment is not desirable in terms of "atom economy,"[2] but the latter is also not technically easy to realize. Another problem emerges from the use of base or acid catalysts, which are inevitably employed in this reaction. With such catalysts, many functional groups are not tolerated. Furthermore, it is essential to remove the catalyst from the product because contamination of the catalyst residues causes various problems. The ultimate practical transesterification should meet the following requirements: 1) the ester and alcohol reactants are used in a 1:1 ratio, 2) the catalyst is neutral and readily separable from the reaction mixture, 3) no special technology is needed to remove the liberated alcohol, and 4) both conversion and yield are 100%. We report herein a new protocol that almost clears these hurdles.

$$\mathrm{RCOOR' + R''OH \longrightarrow RCOOR'' + R'OH} \qquad (1)$$

The present study has its foundation on our previous finding that tetraalkyldistannoxanes work well as mild transesterification catalysts.[3–10] Although these compounds bear a relatively large inorganic metaloxane skeleton, they are soluble in organic solvents. We ascribed the unique solubility to their dimeric formulation in which the central stannoxane core is surrounded by lipophilic alkyl groups, for example, **1**.[11] This structural feature led us to postulate that the incorporation of fluoroalkyl groups on the surface of the stannoxane core would render the distannoxane molecule soluble in fluorocarbon solvents and thus that the fluorous biphasic technology[12–14] could be utilized.



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The requisite distannoxane **1a** was readily prepared by treating oxide **2**[15] with aqueous HCl [Eq. (2)]. The ^{119}Sn NMR spectrum of **1a** gave rise to two singlets at $\delta = -178.3$ and -202.5, indicative of the dimeric formulation in solution (R = $C_6F_{13}C_2H_4$ in **1**).[16, 17]

$$\underset{\mathbf{2}}{[(C_6F_{13}CH_2CH_2)_2SnO]_n} + n\,HCl \xrightarrow[THF]{} \underset{\mathbf{1a}}{n/2\,[\{Cl(C_6F_{13}CH_2CH_2)_2SnOSn(CH_2CH_2C_6F_{13})_2Cl\}_2]} \qquad (2)$$

This compound is virtually insoluble in most organic solvents except CH_2Cl_2 (slightly soluble), ethyl acetate, and acetone (highly soluble). On the other hand, its solubility in fluorocarbons is good, for example, 41 g L^{-1} in perfluorohexanes (FC-72, 3M). The partition coefficients (FC-72/organic solvent) for **1a** are high (toluene 99, CH_2Cl_2 99, methanol 49) in marked contrast to the low partition coefficient of oxide **2** (toluene 1.9).[15] Apparently, the increased fluorophilic character of **1a** is induced by the $C_6F_{13}C_2H_4$ groups at the surface, which hamper the exposure of the stannoxane core to the surroundings.

A novel fluorous biphasic transesterification technology has been established with this new catalytic species. As described above, the employment of the reactants in a 1:1 ratio is ideal. To the best of our knowledge, an ultimate stoichiometry that leads to high conversions has not yet been

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