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# Studies in multidrug resistance reversal: a rapid and stereoselective synthesis of the dihydroagarofuran ring system

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**Abstract**—Several dihydroagarofuran esters have been reported to be effective multidrug resistance (MDR) reversing agents for both cancer cells and bacteria. We report a rapid synthesis of the dihydroagarofuran ring system from carvone in a sequence that is highlighted by a sequential conjugate addition/aldol sequence, a ring closing metathesis reaction, and a diastereoselective alkene reduction to provide an axial methyl group. The synthesis allows for differential esterification reactions as required to study the roles of these groups in MDR reversal.


Multidrug resistance (MDR) is an insidious development in the treatment of cancer and infectious diseases that renders agents of a broad range of structural classes ineffective.[1] While many causes of multidrug resistance have been identified,[2] a common source is the overexpression of ATP-driven pumps in cell membranes that expel drugs before they can diffuse into the cytoplasm and perform their functions.[3] P-glycoprotein (P-gp) is an 170 kDa member of this protein class that is of particular importance in cancer chemotherapy, with an estimated 50% of refractory cancers overexpressing this pump.[4] In their search for P-gp inhibitors, Lee and co-workers identified[5] a series of esters of the dihydroagarofuran ring system that act synergistically with cytotoxic agents such as paclitaxel to inhibit proliferation of cancer cells that overexpress P-gp (Fig. 1). Subsequently Gamarro and co-workers reported[6] that dihydroagarofuran esters inhibit a related ATP-driven bacterial drug efflux pump. These observations suggest that the dihydroagarofuran core could serve as a general scaffolding for the development of a range of MDR-reversing agents. In conjunction with our program in this area we report our studies on a rapid entry into the dihydroagarofuran ring system[7] that allows for differential peripheral functionalization as required for the development of P-gp inhibitors and other MDR-reversing agents.

We envisioned (Fig. 2) the tricyclic dihydroagarofuran ring system (**4**) to arise from an acid-mediated ring closure of a hydroxy alkene such as **5**. The decalin can be formed from a ring closing metathesis reaction of diene **6**. A conjugate addition/aldol reaction between 3-butenal (**7**) or a functional equivalent and a carvone

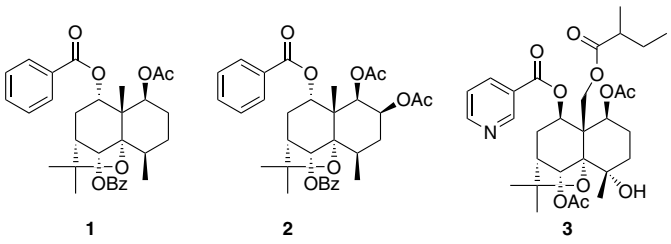


**Figure 1.** Dihydro-β-agarofuran multidrug reversing agents.

*Keywords*: Multidrug resistance; Conjugate addition/aldol; Metathesis; Acylation.
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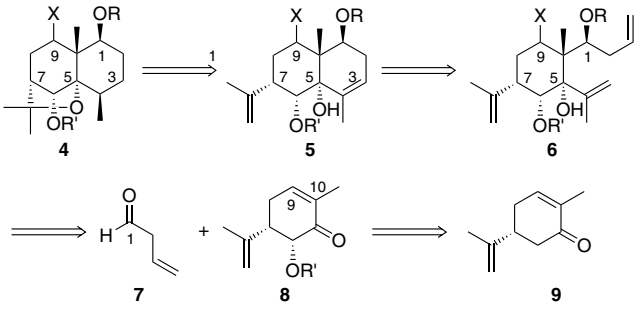
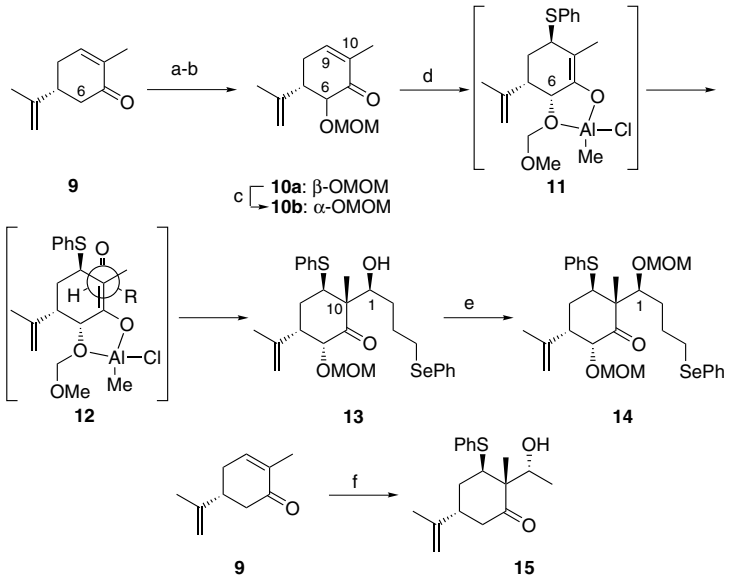


**Figure 2.** Synthetic approach to the ring system.

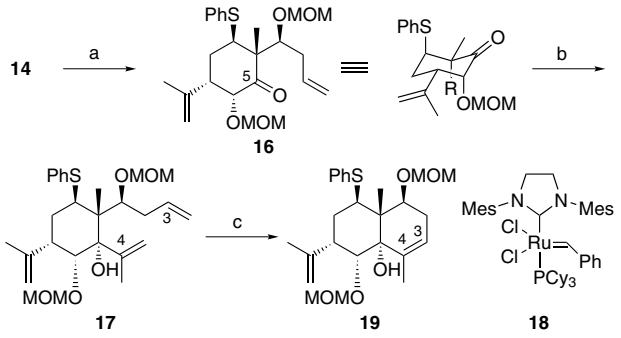
derivative (**8**) and can serve to form the C1–C10 bond while establishing the stereocenters at these sites. The low cost of carvone (**9**) in homochiral form makes it an attractive starting material for this sequence.[8]

Oxygenation was introduced at C6 (Scheme 1) through a Rubottom oxidation[9] of (*R*)-(−)-carvone. The resulting diastereomeric mixture of alcohols **10a**,**b** was efficiently protected with MOMCl and *i*-$Pr_2NEt$. While this sequence is not stereoselective the inexpensive starting material, good chemical yield, and ability to invert the stereochemistry of the undesired isomer through a deprotonation/kinetic reprotonation sequence provide access to sufficient quantities of material for further studies. To construct the C1–C10 bond and to introduce versatile functionality at the C9 position we exposed **10b** to MeAl(Cl)SPh to generate aluminum enolate **11**.[10] While 3-butenal proved to be too unstable for coupling to **11**, 4-phenylselenobutanal, prepared in two steps from $\gamma$-butyrolactone,[11] reacted to provide a 51% yield (based on recovered starting material) of **13** as a 6:1 mixture of diastereomers at C1. Protection of the C1 hydroxyl group as a MOM ether proceeded under standard conditions in nearly quantitative yield and without stereomutation through retroaldol chemistry to yield **14**. The stereochemical outcome of the aldol reaction cannot be explained through a Zimmerman–Traxler transition state. We postulate that the aluminum enolate coordinates to the C6 oxygen to disfavor productive aldehyde coordination, making open transition state **12** more energetically favorable. Consistent with this explanation, exposing carvone to MeAl(Cl)SPh and acetaldehyde smoothly provided aldol adduct **15** as a single stereoisomer, consistent with the expected Zimmerman–Traxler model. Attempts to improve the extent of conversion for the aldol reaction were unsuccessful. Monitoring the thiolate addition by NMR showed that the enolate and enone exist in equilibrium, and that at prolonged reaction times the mixture reverts exclusively to the enone, presumably due to disulfide formation by trace amounts of $O_2$. The use of aliphatic sulfides did not provide higher product yields, but did lead to starting material decomposition. Attempts to trap the enolate as an enol silane through Evans' method[12] ($PhSSiMe_3$, $Bu_4NCN$) resulted in starting material recovery.

In preparation for the ring closing metathesis reaction, selenide oxidation and elimination was effected through exposure of **15** to *m*-CPBA at −78 °C followed by heating in the presence of dihydropyran and pyridine to form **16** in excellent yield. Introducing the other olefin was achieved with a diastereoselective addition of isopropenylmagnesium bromide into the hindered C5 ketone to form diene **17**. We propose that the stereocontrol in this process can be attributed to steric shielding of the bottom face of **16**, which would be expected to be the more reactive conformer based on the Felkin–Anh model. Quenching this reaction with $D_2O$ resulted in deuterium incorporation at C6, indicating that enolate



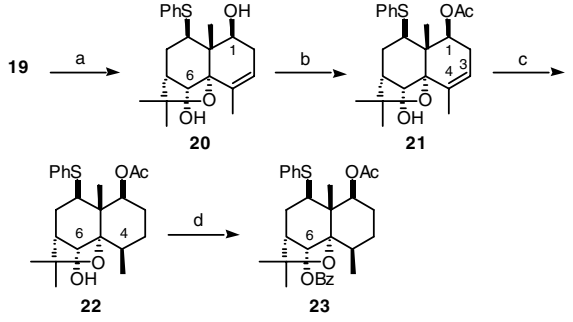
**Scheme 1.** Conjugate addition/aldol sequence. Reagents and conditions: (a) i. LDA, THF, TMSCl, −78 °C, ii. *m*-CPBA, $NaHCO_3$, $CH_2Cl_2$, iii. HF, MeOH, 63%, *anti*:*syn* = 5.5:1; (b) MOMCl, DMAP, *i*-$Pr_2NEt$, $CH_2Cl_2$, 40 °C, 99%; (c) LDA, THF, −78 °C, 92%, **10a**:**10b** = 1:3; (d) $Me_2AlCl$, PhSH, $CH_2Cl_2$, −50 °C, then **10b**, then 4-phenylselenobutanal, 51% (borsm); (e) MOMCl, DMAP, *i*-$Pr_2NEt$, $CH_2Cl_2$, 40 °C, 95%; (f) $Me_2AlCl$, PhSH, $CH_2Cl_2$, −50 °C, then **9**, then $CH_3CHO$.




**Scheme 2.** Construction of the B-ring. Reagents and conditions: (a) *m*-CPBA, $CH_2Cl_2$, −78 °C, then pyridine, DHP, reflux, 97%; (b) isopropenyl magnesium bromide, THF, rt, 80% (borsm); (c) **18**, $CH_2Cl_2$, reflux, 94%.

formation competes with nucleophilic addition, and reprotonation is facially selective for starting material regeneration. The use of isopropenylcerium dichloride was not effective at increasing conversion. In consideration of the sulfide group in **17** we selected the second generation Grubbs metathesis catalyst (**18**)[13,14] to perform the ring closing reaction. Exposing **17** to 2.5 mol% of this catalyst provided didehydrodecalin **19** in 94% yield within 15 min at 40 °C. $^1$H NMR analysis of **19** allowed us to confirm the stereochemistry of the Grignard addition and established that the A-ring exists in a twist boat conformation (Scheme 2).

The twist boat conformation in **19** places the isopropenyl group relatively far from the angular hydroxyl group for facile etherification. In analogy to White's work on this ring system,[15] triflic acid in THF was required to effect the desired ring closure and concomitant methoxymethyl ether deprotection to form tricycle **20** in 30% yield. Weaker acids failed to effect the cyclization, and the use of $CH_2Cl_2$ as a non-basic solvent resulted in complete decomposition. Given the differences in the steric environments around the C1 and C6 hydroxyl groups, we felt that selective acylation at C1 could be achieved. Indeed, exposure of **20** to standard acylation conditions ($Ac_2O$, pyridine, DMAP, $CH_2Cl_2$, rt) selectively provided ester **21** in 56% yield. The C6 hydroxyl group proved to be quite inert toward acylation, presumably because of steric shielding by the vinylic methyl group. Therefore we reduced the C3–C4 olefin with Crabtree's catalyst[16] and $H_2$ in order to exploit coordination from the C5 oxygen for facial control. This reaction provided **22** as a single diastereomer with the correct stereochemistry at C4, as determined by an NOE between the C6 hydrogen and the C4 methyl group, thus completing the enantio- and diastereoselective synthesis of the dihydroagarofuran ring system. While the C6 hydroxyl group still proved to be difficult to acylate, efficient benzoylation was achieved with BzOTf[17] and pyridine in $CH_2Cl_2$ (Scheme 3).




**Scheme 3.** Completion of the ring system. Reagents and conditions: (a) TfOH, THF, 30%; (b) $Ac_2O$, py, DMAP, $CH_2Cl_2$, 56%; (c) $[Ir(cod)py(PCy_3)]PF_6$, $H_2$, $CH_2Cl_2$, 65% (borsm); (d) BzOTf, py, $CH_2Cl_2$, −78 to 0 °C, 100%.

We have demonstrated that the dihydroagarofuran ring system can be prepared rapidly from carvone. Key steps in this sequence include a conjugate addition/aldol reaction to introduce functionality at C9, form the C1–C10 bond, and set the stereocenters at C1 and C10 with good control, a diastereoselective Grignard addition to set the stereochemistry of the tertiary alcohol at C5, a ring closing metathesis reaction to form the didehydrodecalin ring system, and a facially selective hydrogenation to set the stereochemistry at C4. The reactivity of the C1 and C6 hydroxyl groups is dramatically different, allowing for facile differentiation in acylation reactions as required for a flexible approach to studying the roles of the various ester groups in modulating the activity of P-gp and other ATP-driven pumps with relevance to multidrug resistance.

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## Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2004.08.041. Experimental procedures and spectral data for all reaction products is available.

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