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Article

# A Common Approach to the Synthesis of Monocyclofarnesyl Sesquiterpenes

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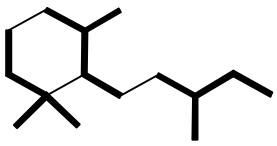
3β-hidroxi-4,4,10β-trimetil-9-decalona e seu análogo deshidroxi são intermediários úteis cuja oxidação de *Baeyer-Villiger* e subsequente homologação por dois carbonos propicia a construção rápida do esqueleto monociclofarnesólico. Os estudos sintéticos visando a uma variedade de sesquiterpenos são discutidos.

3β-hydroxy-4,4,10β-trimethyl-9-decalone and its dehydroxy analogue are useful intermediates whose *Baeyer-Villiger* oxidation and subsequent two-carbon homologation provides a quick entry into the monocyclofarnesyl skeleton. The synthetic approaches to a variety of sesquiterpenes are discussed.

**Keywords:** Baeyer-Villiger *reaction, monocyclofarnesyl, sesquiterpenes, aplysistatin, ambilol, 7-hydroxy-6,11-cyclofarnes-3(15)-en-2-one, ancistrofuran, synthesis*

## Introduction

Sesquiterpenes having a monocyclofarnesyl skeleton **1** are ubiquitous in nature[1].



**1**

In such natural products the trimethylsubstituted ring is often additionally functionalized in the C3-neopentyl position (*e.g.* **2 - 4**) as well as at the methyl-bearing tertiary carbon atom (*e.g.* **2 - 7**[#]). In view of the placement of functionality in the well known *trans*-decalones **8a**[2] and **8b**[2a,3] it was quite obvious that they could serve a role as common starting materials for many monocyclofarnesyl-sesquiterpenes syntheses. More specifically, *Baeyer-Villiger* oxidation of the B-ring ketone would provide **9a/b** containing the correctly functionalized carbocyclic ring with appropriate stereochemistry for a variety of natural products. Introduction of two carbons atoms α to the lactone-carbonyl (alternatively in the open chain form) would complete the construction of the monocyclofarnesyl skeleton, (Scheme 1).

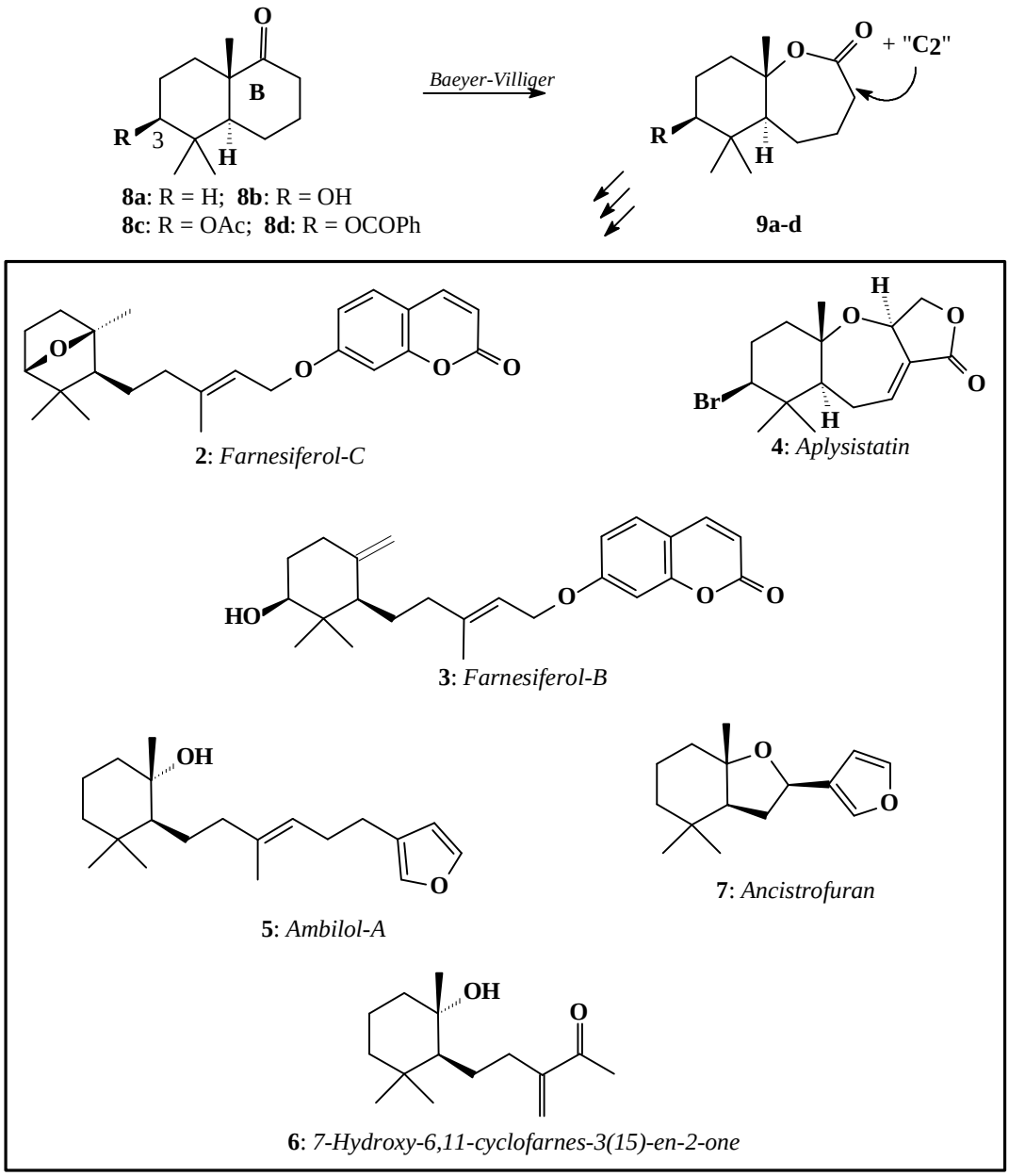
We are currently engaged in using this strategy for the synthesis of several sesquiterpenes. Recently we disclosed the total synthesis[4] of (±)-*farnesiferol-C* **2** which closely followed along these lines. Here we would like to present a review and update on our ongoing efforts to synthesize *aplysistatin* **4**[5], *ambilol-A* **5**[#6], *7-hydroxy-6,11-cyclofarnes-3(15)-en-2-one* **6**[7] and *ancistrofuran* **7**[8].

## Results and Discussion

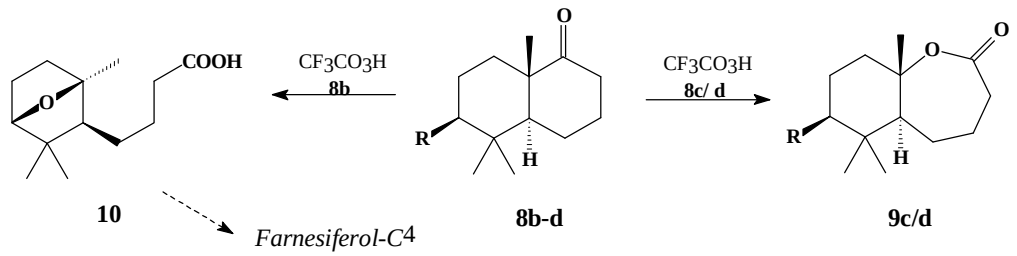
At the outset, the abovementioned *Baeyer-Villiger* oxidation of the 9-decalone system deserves some comment.

[#] *Ambilol-A* **5** is not a sesquiterpene. However, its' C1-C15 "monocyclofarnesyl-subskeleton" is clearly amenable to synthesis according to the strategy under discussion.

The apparently straightforward B-ring ketone oxidation to the ε-lactones **9a/b** bore some surprises. Thus, performing the oxidation on the hydroxy ketone **8b** provided the unconventional product **10** arising through participation of the 3β-hydroxy group. Substrates bearing an acid labile OH protecting group which is removed under the *Baeyer-Vil-*




**Scheme 1.**



*liger* reaction conditions also resulted in **10** whereas the stable 3β-acyloxy derivatives **8c/d** gave the expected lactones **9c/d**[4].

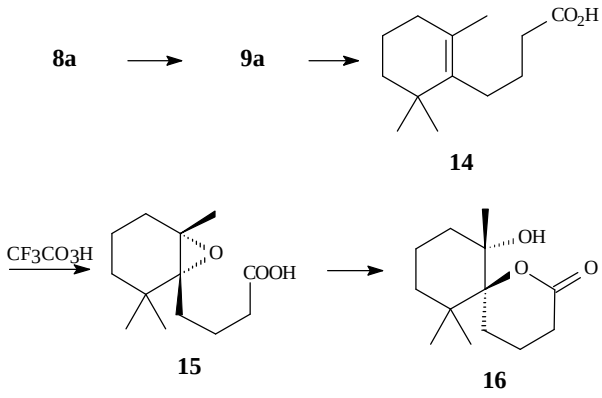
The mechanism of this rearrangement is currently the subject of investigation. Thus, the question of whether transanular oxa-ring formation occurs stepwise (**8b** → **9b** → **12** → **10**) or in a concerted fashion with direct participation of the 3β-hydroxyl (**8b** → **13** → **10**) is being addressed by us by means of a computational analysis of the thermodynamic and kinetic aspects of the possible reaction paths[9] (see Scheme 2).

The 3-methylene analogue **8a** gave an equally surprising product upon *Baeyer-Villiger* oxidation in acidic media ($CF_3CO_3H/CF_3CO_2H/CH_2Cl_2$), namely the hydroxy spirolactone **16**[10]. Controlled buffered conditions ($CF_3CO_3H/CF_3CO_2H/Na_2HPO_4/CH_2Cl_2$/0 °C, 72% or *m*-CPBA/$NaHCO_3$/DCE/RT-reflux, 74%) were necessary to avoid the formation of **16** and secure the desired lactone **9a**. We propose, that in acidic media **9a** proceeds via olefin **14** and epoxide **15** to **16** (see Scheme 3).

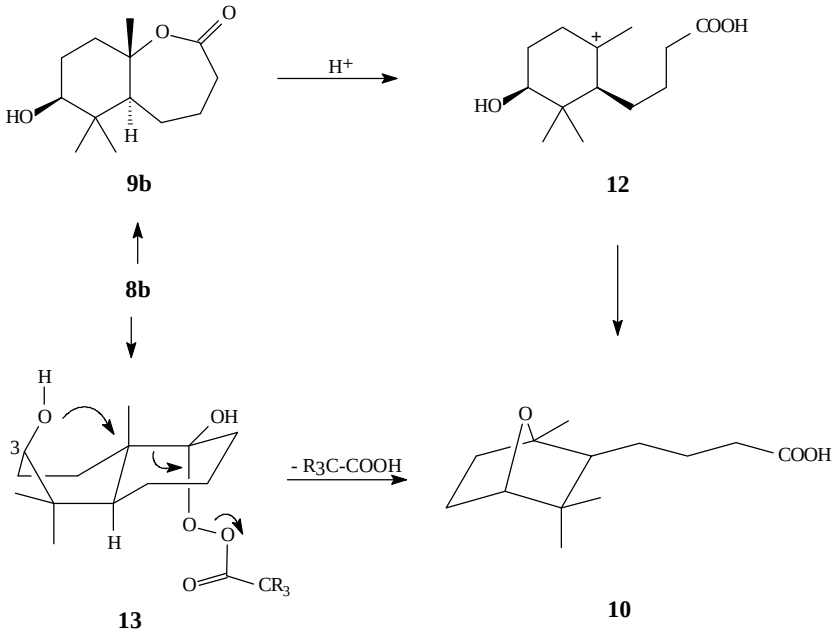
Whilst the interesting rearrangement in the *Baeyer-Villiger* reaction of **8b** giving **10** allowed the synthesis of *farnesiferol-C* **2**[4], the other (lactone) products in hand (**9a** and **9c/d**) open the way for our synthetic approaches to the natural products **4 - 7**.

The decalones **8a/b** are prepared[2,3] from the well known Wieland-Miescher ketone **17**[11] which has served as starting material in many syntheses[2a,2b,3a,4,12]. The advent of the availability of the Wieland-Miescher ketone in enantiomerically pure form[13] has widened its scope so as to permit the synthesis of natural products in their optically pure state[14]. We have recently found an improved and very efficient method for a rapid, selective and high-yielding preparation of the monoketal **18** of this diketone, uncontaminated by bisketal (which is extremely tedious to separate!)[15]. In summary, these developments allowed an expedient preparation of the common decalone intermediates **8a-d** in appreciable quantity along established lines[3b] and in optically pure form.

The decalone **8d** was oxidised using trifluoroperoxyacetic acid / trifluoroacetic acid in dichloromethane providing exclusively the lactone **9d** in 75% yield. The final two carbons of the monocyclofarnesyl skeleton were then incorporated by alkylation of the lithium enolate (LDA/TMEDA/THF/-78 °C) with 1,2-dibromoethyl ethyl ether, cleanly providing the ethoxyethylated product **19d** (79%) as a 2:1 mixture of diastereoisomers. Although the stereochemistry at the alkylated carbon in **19d** was of no consequence for subsequent synthetic manipulations, the alkylation was shown to have occurred exclusively from



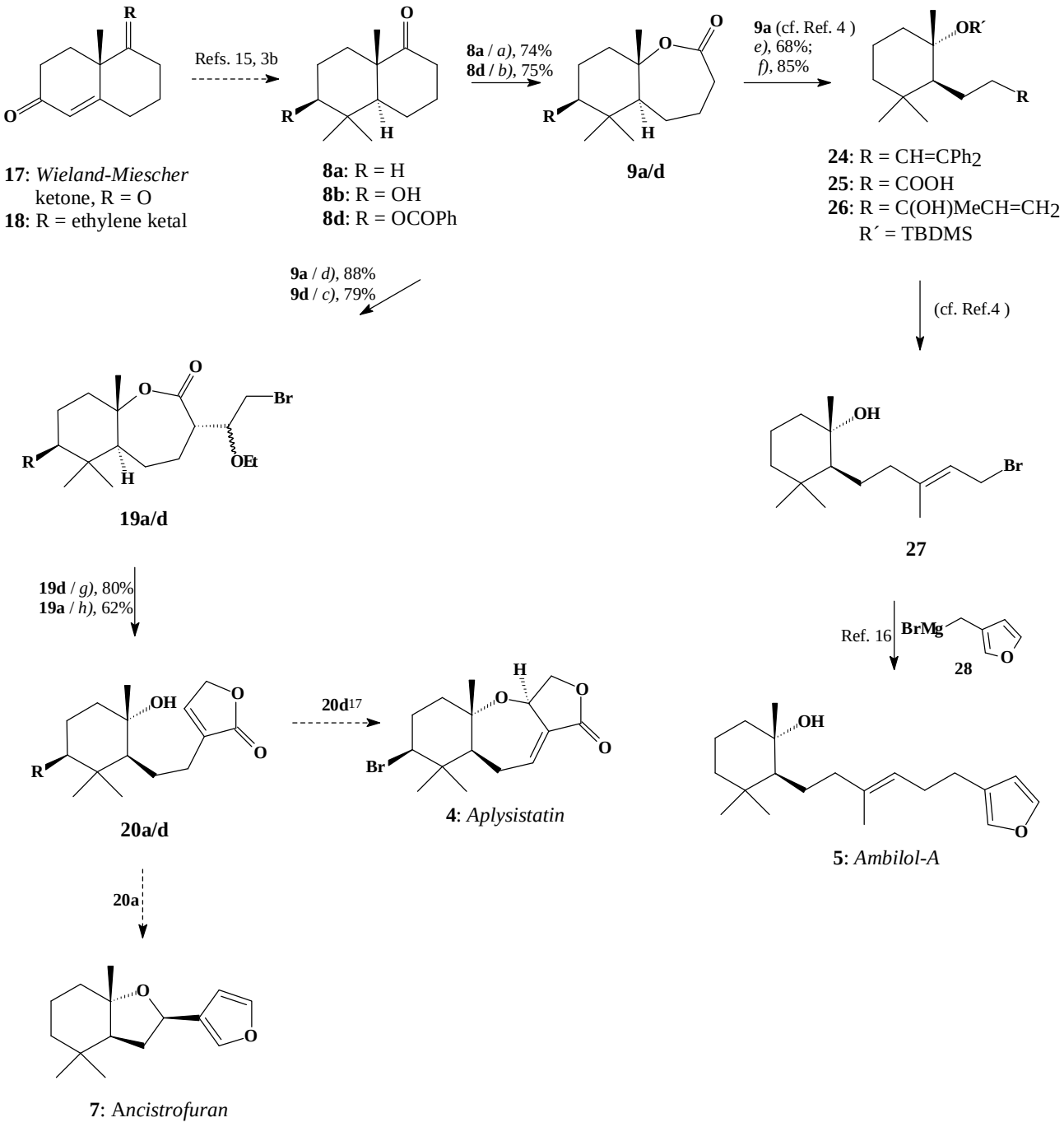

**Scheme 3.**




**Scheme 2.**

the α-face (opposite to the angular methyl substituent) by means of an X-ray crystal structure of the minor diastereomer; (Fig. 1).

With a conclusive structure proof of the C-15 monocyclofarnesyl skeleton now in hand, the mixture of diastereomers **19d** was treated with 5% aqueous $K_2CO_3$ in THF/acetone resulting in a one-pot conversion to the hydroxy butenolide **20d** involving ε-lactone hydrolysis, butyrolactone formation of the intermediate γ-bromo acid and β-ethanol elimination thus completing the overall transformation of decalone **8d** to the advanced sesquiterpene intermediate **20d** in just three steps and 47% overall yield. The hydroxybutenolides **20** serve as intermediates for *aplysistatin* **4**[17] (from **20d**) and *ancistro-*




**17**: *Wieland-Miescher* ketone, R = O
**18**: R = ethylene ketal

**8a**: R = H
**8b**: R = OH
**8d**: R = OCOPh

**9a/d**

**24**: R = CH=CPh$_2$
**25**: R = COOH
**26**: R = C(OH)MeCH=CH$_2$
R´ = TBDMS

**19a/d**

**27**

**20a/d**

**4**: *Aplysistatin*

**28**

**5**: *Ambilol-A*

**7**: A*ncistrofuran*

**Scheme 4.** *a)* m-CPBA/DCE/$NaHCO_3$/RT-rfx.; *b)* $CF_3CO_3H/CF_3CO_2H/Na_2HPO_4/CH_2Cl_2$/RT; *c)* LDA/THF/TMEDA/EtO-$CHBrCH_2Br$/-78 °C – RT; *d)* LDA/LiCl/THF/DME/EtO-$CHBrCH_2Br$/-78 °C – RT; *e)* $PhMgBr/Et_2O$/0 °C – RT; *f)* p-TsOH/$CHCl_3$/RT; *g)* $K_2CO_3/H_2O$/THF/acetone/60 °C; *h)* $K_2CO_3/H_2O$/THF/60 °C.

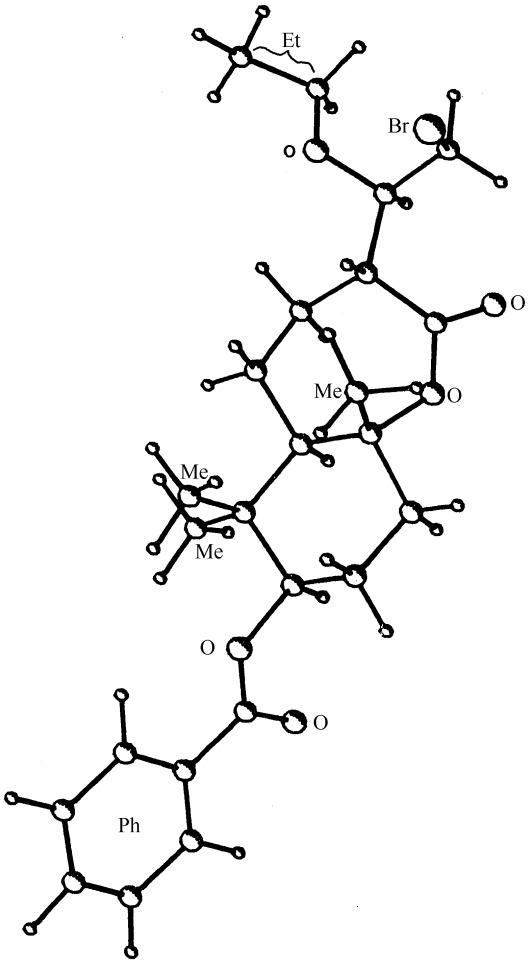
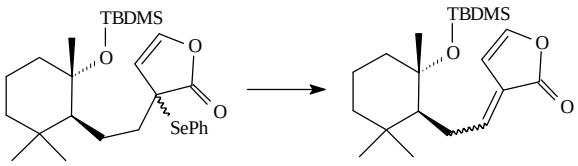


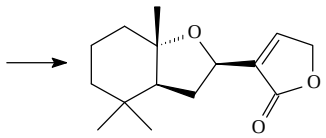

**Figure 1.**

*furan* **7** (from **20a**). The latter compound was prepared in a similar fashion from **8a** in 40% overall yield (see Scheme 4).

Several routes from **20a** to *ancistrofuran* can be envisaged. Our initial results indicate, that phenylselenation of the dienolate derived from the TBDMS-ether derivative gives, albeit in low yield (amongst other products) the deconjugated phenylseleno derivative **21**. Clearly, oxidative elimination of this compound will provide the exocyclic α,β-unsaturated lactone **22**, deprotection and ring closure of which would result in the butenolide **23** which has been previously converted to *ancistrofuran*[8g]. Therefore the transformation of **21** into **23** would complete a formal total synthesis of *ancistrofuran*. At the time of writing, our efforts in this regard are continuing and we will report the results at an appropriate opportunity. Owing to the fact, that the absolute configuration of *ancistrofuran* is not known, we are in a position to answer this question by virtue of the use of chiral material stemming from the (+)-Wieland-Miescher ketone.




**21** **22**




**23** ( + epimer )

If the introduction of the final two carbon atoms of the monocyclofarnesyl skeleton is delayed until a later point in the synthetic sequence, one may open the way to *farnesiferol-C* **2**[4], *ambilol-A* **5** and *7-hydroxy-6,11-cyclofarnes-3(15)-en-2-one* **6**[17]. In a procedure analogous to that used for the synthesis of *farnesiferol-C*,[4] a standard Barbier-Wieland approach (PhMgBr / $Et_2O$ then *p*-TsOH / $CHCl_3$) provided diphenylolefin **24** from lactone **9a**. At the time of deadline for submission we are involved in the oxidative cleavage of this compound to the hydroxy acid **25**. Treatment of this intermediate with methyllithium followed by TBDMS protection and vinylmagnesium bromide addition (final two monocyclofarnesyl carbons) should result in the allylic alcohol **26**[4]. It then remains to prepare the allylic bromide **27**[4] and couple it with the 3-methylfuran Grignard reagent **28**[16] in order to complete the synthesis of *ambilol-A*.

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17. Our work involving the synthesis of this natural product will be the subject of a future paper.