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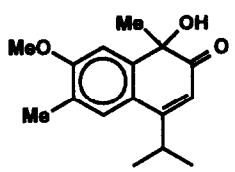
Oxazoline-Mediated Synthesis of the *Gossypium* Sesquiterpene Lacinilene C-7 Methyl Ether and a Structurally Related HIV-1 Reverse-Transcriptase Inhibitor

Thomas G. Gant and A. I. Meyers*

Department of Chemistry, Colorado State University, Fort Collins, Colorado, 80523, U. S. A.

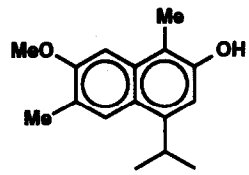
Abstract: *An efficient synthesis of the phytoalexin, lacinilene C-7 methyl ether, via its probable biosynthetic precursor, 2-hydroxy-7-methoxycadalene is described. A related synthesis of a HIV-1 reverse-transcriptase inhibitor is briefly discussed.*

Having recently established a general and efficient method for the synthesis of naphthalenones from naphthyloxazolines,[1,2] it was decided that the next logical step in the development of this chemistry would be an application to a more complex target. Lacinilene C-7 methyl ether[3] (LCME), **1** was chosen for this purpose due to its demonstrated biological activity[4] as well as its striking similarity to a new class of anti-HIV compounds, **2**, recently discovered in this laboratory.[5]



1

2, R = H, Me, iPr



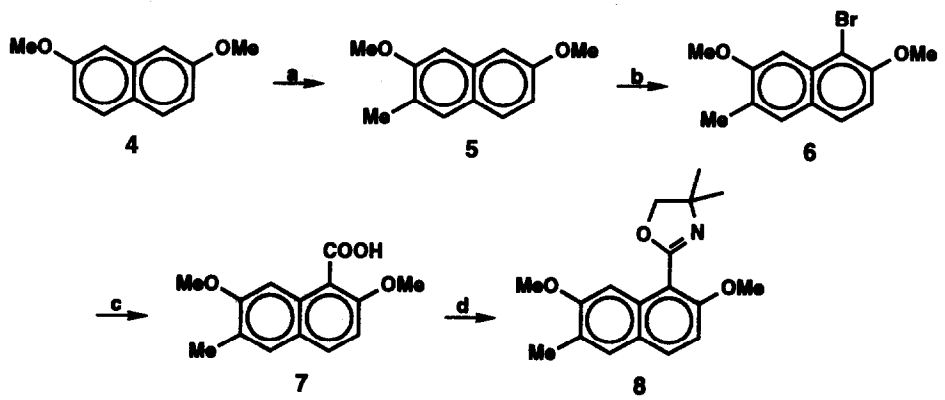
3

LCME (**1**) has been synthesized previously[6] and has been the subject of numerous biological studies owing to its demonstrated activity in mammalian as well as bacterial cells. Isolated from various *Gossypium* species since 1975,[7] this substance has been shown to be the causative agent in the debilitating disease byssinosis, a malady common among workers in the textile industry. The synthetic route chosen intercepts the final step of a previous synthesis passing through another natural product, 2-hydroxy-7-methoxycadalene (HMC),[8] **3**.

The starting material for the synthesis of **1** was the commercially available 2,7-dimethoxynaphthalene, **4**. Introduction of the methyl group at C-6 to produce the trisubstituted naphthalene **5** was achieved via CIPE-controlled o-lithiation of the symmetric substrate **4** followed by treatment with methyl iodide (Scheme 1). Aromatic ring metallation, regiospecific for electronic as well as steric reasons, was accomplished with n-, s-, or t-BuLi in THF at -78°C. Subsequent bromination of **5** in glacial acetic acid gave the requisite tetrasubstituted naphthalene, **6**, in excellent overall yield. The bromide was converted to the carboxylic acid, **7**, by transmetallation

with n-BuLi (1.0 equiv.) or t-BuLi (2.0 equiv.) followed by addition of crushed dry ice (large excess). The acid **7** was then transformed into the acid chloride (thionyl chloride or oxalyl chloride) and converted to the hydroxyamide upon addition of the amino alcohol (2.0 equiv.). Subsequent addition of thionyl chloride (4.0 equiv.) produced the naphthyloxazoline, **8**.

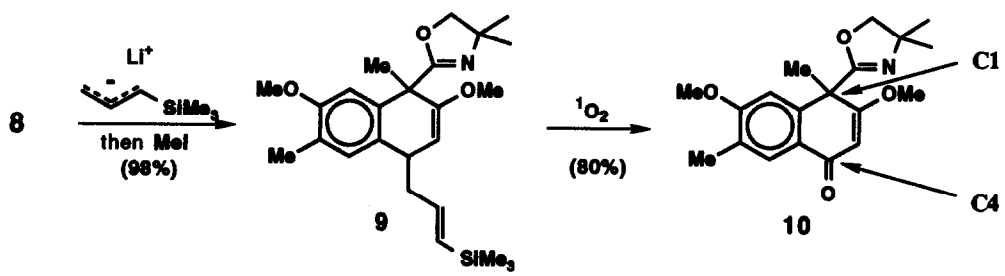
Scheme 1



Key: a. i. sBuLi/THF, ii. MeI (99%); b. Br_2/HOAc (98%); c. i. BuLi/THF, ii. $CO_{2(s)}$ (95%); d. i. $(COCl)_2/CH_2Cl_2$, ii. $NH_2C(CH_3)_2CH_2OH$, iii. $SOCl_2$ (73%).

In accord with prior results,[2] addition of trimethylsilylallyllithium to **8** in THF followed by a methyl iodide quench of the intermediate azadienolate gave a single diastereomer, **9**, in excellent yield. The earlier tandem addition was reported[2] to occur in an *anti*-sense based on transition-state analysis as well as X-ray analysis of one of the adducts. Subsequent oxidation with singlet oxygen in toluene afforded the naphthalenone, **10**. Hence, the allyllithium species acts as a transient functionality, allowing functionalization of C-1 as well as C-4.

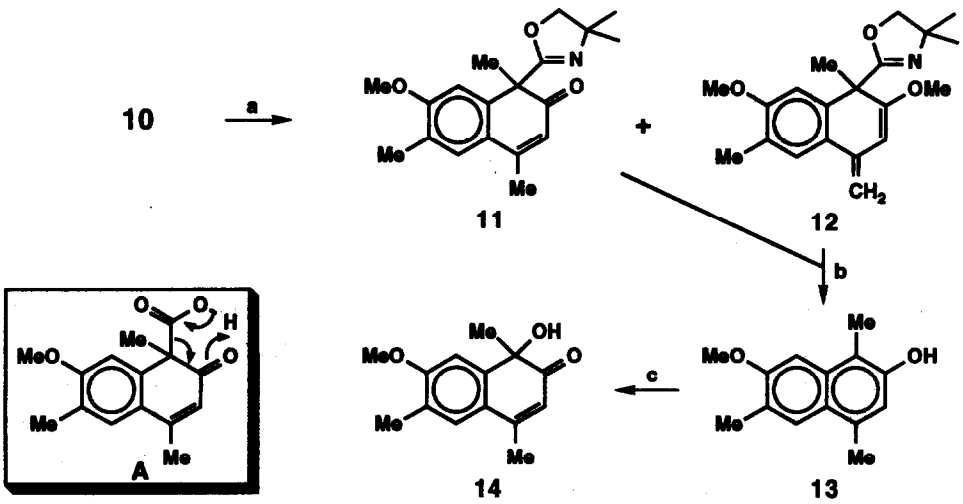
Scheme 2



A sample of **10** was converted to **11**, (an analogue of the HIV-1 active compound, **2**), and **12** through an alkylative transposition of the β-methoxy-enone functionality (Scheme 3). It is noteworthy that **11** was found to possess reverse-transcriptase inhibition properties virtually identical to the less functionalized prototype,[9] **2**. Hydrolysis of both **11** and the concomitant

product **12** under strongly acidic conditions (6N HCl, 3h) gave the aromatized HMC analogue **13**. This pentasubstituted naphthalene was not unexpected; efficient avoidance of this facile transformation was addressed in a previous report.[2] The aromatization is believed to arise through decarboxylation of intermediate **A**. The naphthol **13** was then transformed into LCME analogue **14** using diphenylseleninic anhydride.[6a]

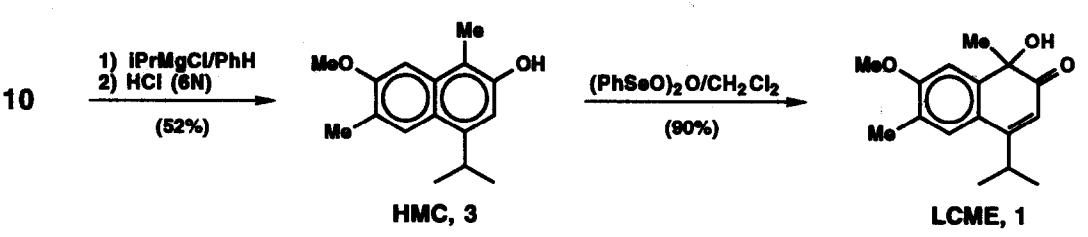
Scheme 3



Key: a. i. MeLi/THF; b. HCl (6N)/THF; c. $(PhSeO)_2O/CH_2Cl_2$.

The synthesis of LCME, **1**, requires the presence of an isopropyl group at C-4 (refer to Scheme 2). The 1,2-addition product between **10** and isopropylmagnesium chloride did not hydrolyze upon aqueous work-up to give the isolable transposed enone as in the example above. Any conditions capable of hydrolysis led ultimately to a cascade of events culminating in the dealkylation and aromatization of the intermediate to give a 52% yield of the naturally-occurring sesquiterpene, HMC, **3** (Scheme 4). This has been transformed to LCME, **1**, through oxidation using diphenylseleninic anhydride[6a] and the earlier procedure was successfully repeated.

Scheme 4



The overall yield of **1** from **4** (24%) competes well with earlier syntheses.[6] In addition, this route allows potential flexibility in the preparation of analogues of LCME as well as HIV-RT inhibitors. An asymmetric variant of this synthesis that precludes the aromatic intermediate **3** is under development.[10]

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8. Stipanovic, R. D.; Greenblatt, G. A.; Beier, R. C.; Bell, A. A. *Phytochemistry* **1981**, *20*, 729.
9. All assays for bioactivity have been carried out by Dr. Pin-Fang Lin and co-workers at Bristol-Myers Squibb.
10. LCME has been isolated from *Gossypium* in both racemic and non-racemic form. It has been postulated that HMC is converted to LCME through an enzymatic process *in vivo* leading to the non-racemic form. Racemic LCME is then the product of autoxidation of HMC. As a consequence, the degree of enantiomeric purity of the natural isolates is a function of the source of the plant material and the methods used to obtain the compound. Much of the interest in LCME stems from its inglorious connection to byssinosis, a clinical syndrome associated with lung disease. This affliction occurs upon long-term exposure to cotton-trash dust, containing the autoxidized (racemic) form of LCME. The plant is said to use non-racemic LCME to kill bacterial pathogens.

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