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Synthesis of the Guaiane (±)-Alismol Using a Free Radical Fragmentation/Elimination Sequence

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Abstract: The first synthesis of the guaiane alismol (3) is reported. The efficient, stereoselective and regioselective approach involves only eight steps, with the key transformation being a radical fragmentation/elimination sequence which proceeds in high yield (92%).

We reported previously[1] that free radical fragmentation of photoadduct derivatives **1** to yield bicyclic systems **2** (Scheme 1) could have potential applications in the synthesis of natural products. We wish to report the first synthesis of the guaiane alismol (**3**), which was isolated from the crude drug "takusha" (*Alsima plantago-aquatica* var. *orientale*) by Hikino in 1983.[2] Our approach requires only eight steps and includes a novel free radical fragmentation/elimination sequence in the key step.

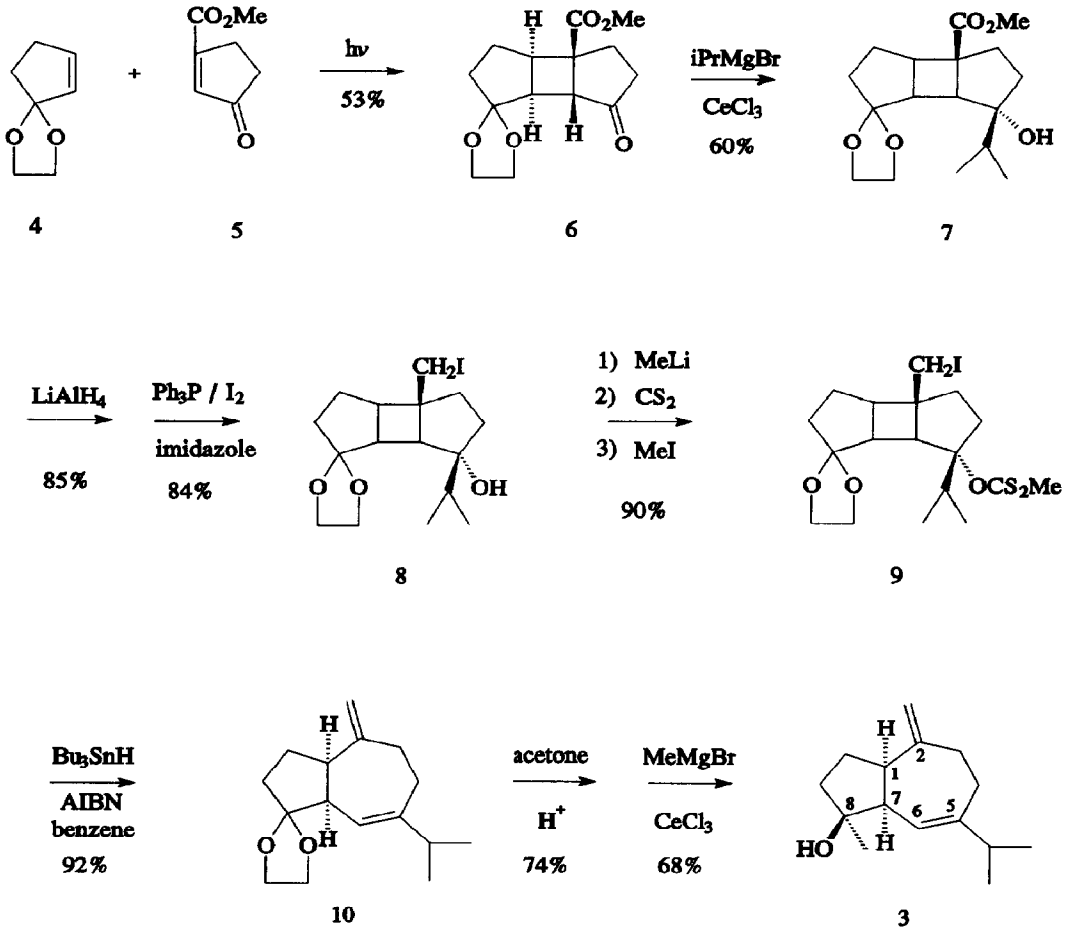
Scheme 1

1 **2**

m, n = 1, 2

In the initial [2+2] photoaddition step, excess ketal **4** (rather than a cycloalkene as used in our earlier studies[1]) was irradiated[3] with enone **5** to give the head-to-head *cis-anti-cis* adduct **6** (Scheme 2). Ketals such as **4** generally give the head-to-head regioisomer as the major or exclusive adduct in photoadditions,[4,5] particularly in non-polar solvents.[6] Regio- and stereoselective addition of isopropylmagnesium bromide to the adduct gave **7** with no significant reaction at the ester group. $CeCl_3$ was included in the reaction mixture to minimize the enolization side reaction.[7] Reduction of the ester group in **7** with $LiAlH_4$ followed by selective reaction of the primary alcohol function using our previously reported I_2/Ph_3P/imidazole protocol[8] gave iodide **8**. Hindered secondary and tertiary alcohols (such as that in **8**) do not react under these conditions.[8] The preparation of the tertiary xanthate **9** was problematic until it was found that methyllithium effectively generated the necessary

Scheme 2


CO2Me
hν
53%
H
CO2Me
iPrMgBr
CeCl3
60%
OH
4
5
6
7
LiAlH4
85%
Ph3P / I2
imidazole
84%
CH2I
1) MeLi
2) CS2
3) MeI
90%
OCS2Me
8
9
Bu3SnH
AIBN
benzene
92%
acetone
H+
74%
MeMgBr
CeCl3
68%
HO
10
3

alkoxide in the first step.

With iodo xanthate **9** in hand, we now had a substrate to investigate the desired fragmentation/elimination sequence, i.e. abstraction of the iodide would initiate the fragmentation and the xanthate would serve as the leaving group. Xanthates, halides, and groups such as SPh, SOPh, SO_2Ph and SePh have been shown to be effective radical leaving groups[9] and a tandem radical cyclization/elimination sequence has been used in the formation of a cyclopropane ring[10] and of 5-membered heterocycles.[11] But, we are not aware of any report of a fragmentation/elimination sequence being employed in a synthetic sequence to generate a new unsaturated ring. In the event, treatment of **9** with Bu_3SnH under standard radical conditions gave in excellent yield the desired diene **10**. During this reaction a methylene group was introduced at C2, fragmentation gave a *cis*-fused 7-membered ring and the C5-C6 double bond was introduced regioselectively. All these structural features are present in the target molecule **3**. To complete this first total synthesis of the sesquiterpenoid, the ketal function in **10** was removed using a transketalization procedure with acidic acetone and the resultant ketone was reacted stereoselectively on the less hindered α-face with methylmagnesium bromide to give (±)-alismol **3** in good yield. The Grignard reaction was conducted in the presence of $CeCl_3$ again to minimize enolization and to prevent the possible migration of the C5-C6 double bond into conjugation with the C8 ketone. A comparison of the spectral data for the racemic synthetic product with optically active **3**[2] confirmed their structural identity.[12] The absolute configuration of natural (+)-alismol has not been established, but with our previously reported photochemical asymmetric induction methodology[5] and the use of a chiral ketal in the initial photoaddition step, it should be possible to make this determination and to synthesize optically enriched **3**.

This regioselective and stereoselective synthesis of (±)-alismol **3** was accomplished in only eight steps, with the critical step being a new free radical fragmentation/elimination sequence. A systematic investigation of this tandem methodology and its use in the synthesis of other natural products is currently under investigation.

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12. The following 400 MHz NMR spectral data for our synthetic product were compared with the 100 MHz data reported for the natural product:[2] ^{1}H NMR($CDCl_3$) δ 5.57(s, 1H, =CH), 4.78(s, 1H, $=CH_2$), 4.72(s, 1H, $=CH_2$), 2.48(m, 1H), 2.00-2.35(m, 6H), 1.50-2.00(m, 5H), 1.25(s, 3H, CH_3), 1.01(d, J=7.0 Hz, 3H, CH_3), 1.00(d, J=7.0 Hz, 3H, CH_3); ^{13}C NMR($CDCl_3$, 100 MHz) δ 153.9, 146.7, 121.3, 106.5, 81.9, 55.0, 47.3, 40.3, 37.4, 37.1, 30.0, 24.7, 24.1, 21.5, 21.3.

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