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SYNTHESIS OF (±)-(3*R**, 4*S**, 4a*R**)-4,8-DIHYDROXY-3-METHYL-3,4,4a,5-TETRAHYDRO-1*H*-2-BENZOPYRAN-1-ONE

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Abstract —The insecticidal tetrahydroisocoumarin, (3*R*, 4*S*, 4a*R*)-4,8-dihydroxy-3-methyl-3,4,4a,5-tetrahydro-1*H*-2-benzopyran-1-one, was synthesized as a racemate using one-pot esterification–Michael addition–aldol reaction of δ-hydroxy-α,β-unsaturated aldehyde and diketene as a key step.

In 1995, Findlay *et al.*[1] isolated a tetrahydroisocoumarin, (3*R*, 4*S*, 4a*R*)-4,8-dihydroxy-3-methyl-3,4,4a,5-tetrahydro-1*H-2*-benzopyran-1-one (**1**, Figure 1), from culture filtrates of conifer endophytic fungi [*Canoplea elegantura* (Cooke) M. B. Ellis 7BS37C1 and 6BS10K1] together with five new compounds and two known isocoumarins (**2**[2] and **3**[3]). Some of these compounds including **1** show toxicity to spruce budworm (*Choristoneura fumiferana* Clem.) larvae (and cells). Because the two known compounds (**2** and **3**) isolated in Findlay's work were identical in spectroscopic characteristics and sign of specific rotation with those previously isolated,[2,3] the C-3 absolute configurations common to these co-metabolites were represented as such. Many of naturally occurring 8-hydroxy-3-methyl-3,4-dihydroisocoumarins (mellein[4] or ramulosin[2,5] derivatives) exhibit a variety of biological activities,[6] but there is no report of toxicity to insects to our knowledge. Aiming at development of efficient method to construct this tetrahydroisocoumarin, we started synthesizing **1** as a racemate. Below, we describe the first synthesis of this compound.

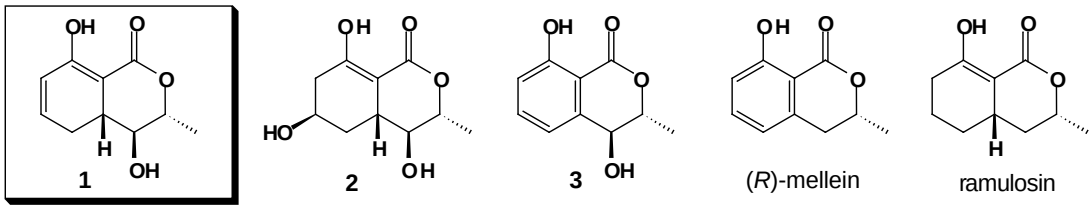
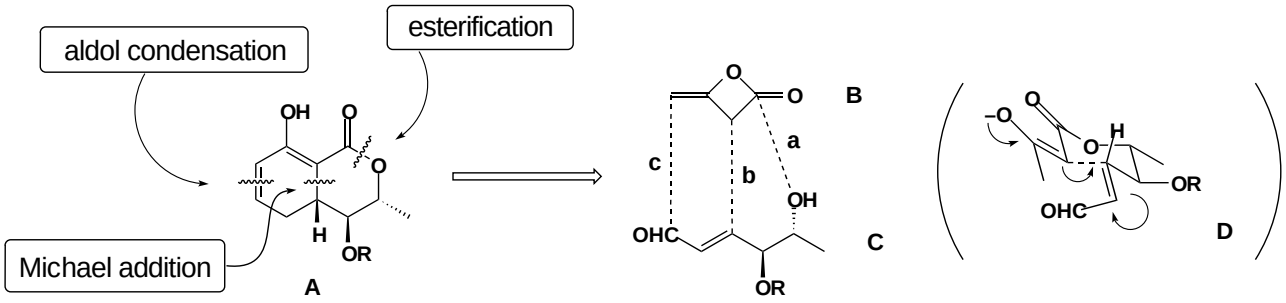


Figure 1.

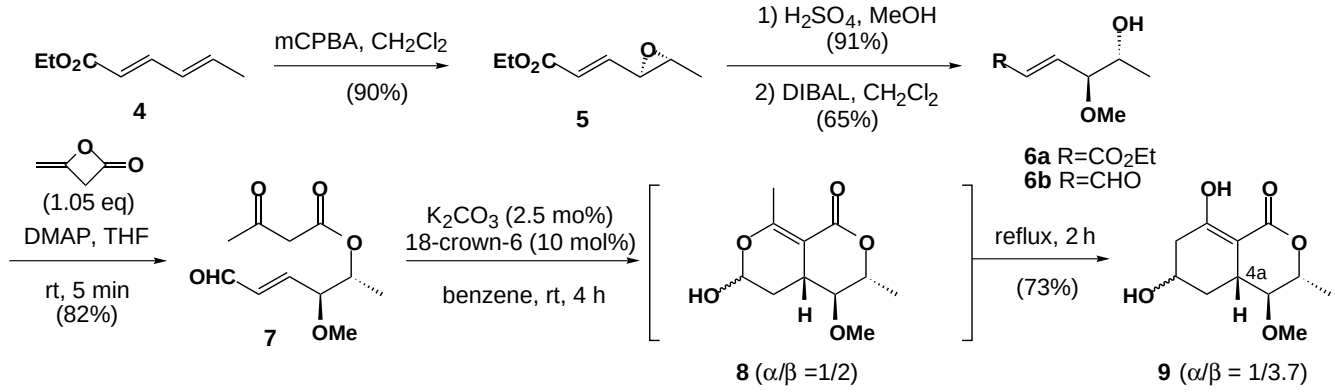
Our synthetic strategy is shown in Scheme 1. The target skeleton (**A**) was thought to be made from two moiety, diketene (**B**) and δ-hydroxy-α,β-unsaturated aldehyde (**C**) by esterification (**a**) at first, then Michael addition (**b**) of enolate generated by opening the diketene β-lactone, and aldol condensation (**c**) of another enolate. In Michael addition step, the angular hydrogen atom will be controlled to be in an



Scheme 1. Synthetic plan of tetrahydroisocoumarin (**1**).

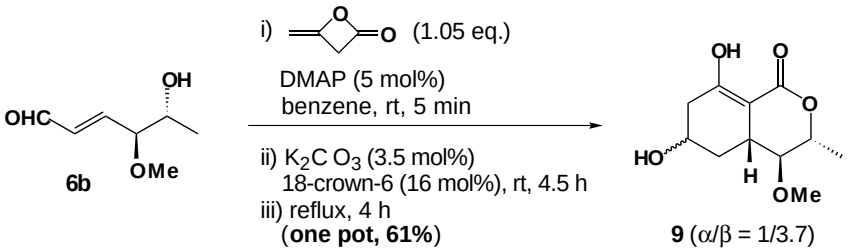
axial direction because of a favored conformation of the transition state (**D**) (the conformation of the six-membered ring refers chair form with substituents all equatorial).

Epoxidation of ethyl sorbate (**4**) using mCPBA at 0°C to room temperature afforded epoxide (**5**) as a colorless oil in 90% yield (bp ~70.0°C / 2 mmHg). Epoxide opening of **5** with sulfuric acid and methanol at room temperature for 1 h gave hydroxy ester (**6a**) (91%, colorless oil, bp 91.0-92.0°C / 1.5 mmHg), whose ester group was reduced with 2 equivalents of diisobutylaluminum hydride at –78°C for 70 min to afford aldehyde (**6b**) in 65% (colorless oil, bp 80.0-84.0°C / 1.5 mmHg). Esterification of **6b** with diketene in the presence of catalytic amount of 4-(dimethylamino)pyridine[7] occurred easily at room temperature to give β-keto ester (**7**) (82%, colorless oil). When **7** was treated with potassium carbonate and 18-crown-6 in benzene at room temperature, desired Michael addition occurred to afford hemiacetal (**8**) (colorless oil, inseparable mixture of α- and β-hydroxy isomers in 1:2 ratio). When the reaction was continued under reflux for additional 2 h, the hemiacetal ring of **8** reopened and aldol reaction proceeded to give the desired bicyclic compound (**9**) in a high yield (73% from **7**, colorless viscous oil, inseparable mixture of α- and β-hydroxy isomers in 1:3.7 ratio).



Scheme 2.

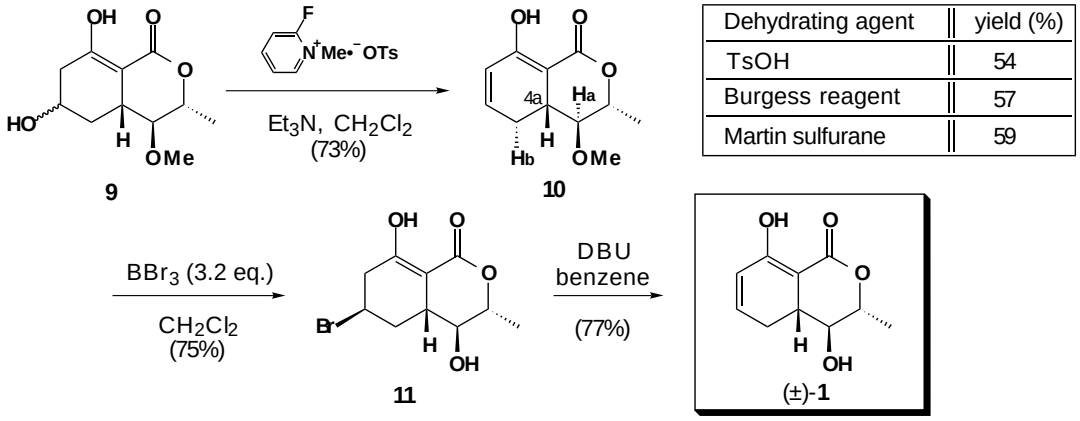
We then tried the one-pot esterification–Michael addition–aldol reaction from **6b** to **9**. The best result is shown in Scheme 3. Using 1.05 equivalents of diketene, esterification proceeded smoothly in benzene. Then the addition of a catalytic amount of potassium carbonate and 18-crown-6 and heating caused the further reactions to give **9** in 61% yield in one-pot. Although some similar methods for preparation of a simple six membered ring have been reported,[8-11] we were not aware of any such applications to construction of a bicyclic system in one-pot with controlling stereochemistry. The stereochemistry at C-4a could not be clarified because **9** was the inseparable mixture and showed a complicated ^{1}H-NMR



Scheme 3.

spectrum, and therefore the determination of its configuration was carried out at the later stage.

As the further dehydration of **9** did not occur under the conditions against our expectation, it was tried in the next step (Scheme 4). Using *p*-toluenesulfonic acid (in benzene, reflux, overnight), Burgess reagent[12] (in benzene, reflux, 2 h) or Martin sulfurane[13] (in chloroform, room temperature, 3 h), the dehydrated product (**10**) was obtained in moderate yields (54-59%), and the best yield was obtained using 2-fluoro-*N*-methylpyridinium tosylate[14] at room temperature for overnight (73% yield, colorless needles, mp 71.5-72.0°C). At this stage, the stereochemistry at C-4a could be determined to be correct as shown in Scheme 4 from the coupling constants (9.6 Hz with Ha, 17.0 Hz with Hb). Treatment of **10** with excess boron tribromide at 0°C gave bromide (**11**) as a colorless solid (75%) *via* the desired demethylation with a concomitant conjugate addition of bromide ion mainly from β-(axial) side. This was easily dehydrobrominated with DBU at room temperature for 15 min to give (±)-**1** as colorless needles (77%, mp 134.0-135.0°C). The ^{1}H- and ^{13}C-NMR spectra were identical with those of natural **1**.[1, 15]



Dehydrating agent	yield (%)
TsOH	54
Burgess reagent	57
Martin sulfurane	59

Scheme 4.

In summary, the insecticidal tetrahydroisocoumarin (**1**) was efficiently synthesized as a racemate. The overall yield was 16% in 7 steps from commercially available ethyl sorbate. The key step, one-pot esterification–Michael addition–aldol reaction from **6b** to **9** proceeded in a high yield to help making tetrahydroisocoumarin skeleton easily. We are now synthesizing optically active **1** by the same strategy using the known epoxide [(*R*, *R*)-**5**][16] in order to confirm the proposed absolute configuration, and are preparing some derivatives for investigating the unique biological activity.

ACKNOWLEDGMENT

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15. The spectral data of synthetic (±)-**1** are shown below. IR (KBr): ν = 3400, 2840, 1650, 1610, 1580, 1410, 1390, 1370, 1345, 1310, 1240, 1190, 1065 cm^{-1}; ^{1}H-NMR (500 MHz in $CDCl_3$): δ = 1.47 (3H, d, *J* = 6.3 Hz, 3-Me), 2.01 (1H, dddd, *J* = 17.0 Hz, 16.8 Hz, 3.0 Hz, 2.2 Hz, 5-Ha), 2.26 (1H, d, *J* = 6.0 Hz, 4-OH), 2.67 (1H, ddd, *J* = 17.0 Hz, 6.0 Hz, 6.0 Hz, 5-Hb), 2.76 (1H, ddd, *J* = 16.8 Hz, 9.8 Hz, 6.4 Hz, 4a-H), 3.46 (1H, ddd, *J* = 9.5 Hz, 9.5 Hz, 6.0 Hz, 4-H), 4.16 (1H, dq, *J* = 9.5 Hz, 6.3 Hz, 3-H), 6.08 (1H, dd, *J* = 9.8 Hz, 3.0Hz, 7-H), 6.51 (1H, ddd, *J* = 9.8 Hz, 6.3 Hz, 2.2 Hz, 6-H), 12.81 (1H, s, 8-OH) ; ^{13}C-NMR (125 MHz in $CDCl_3$): δ = 17.8, 27.6, 37.5, 74.4, 78.1, 90.5, 124.4, 140.3, 169.2, 170.9.
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