

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

Kanako Uchida, Hidenori Watanabe, and Takeshi Kitahara*

Department of Applied Biological Chemistry, Graduate School of Agricultural and Life Sciences,
The University of Tokyo, 1-1-1 Yayoi, Bunkyo-ku, Tokyo 113-8657, Japan

Abstract —The insecticidal tetrahydroisocoumarin, (3*R*, 4*S*, 4*aR*)-4,8-dihydroxy-3-methyl-3,4,4*a*,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*, 4*aR*)-4,8-dihydroxy-3-methyl-3,4,4*a*,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 (mellein⁴ 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.

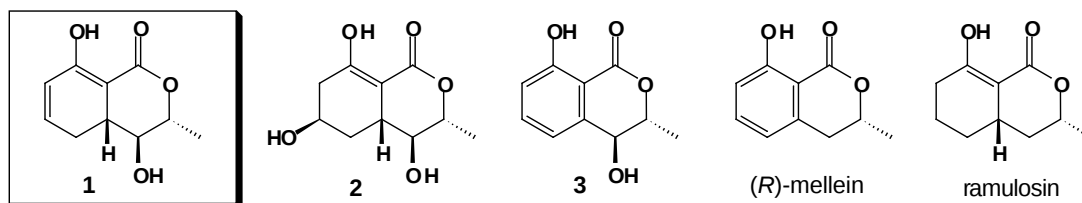
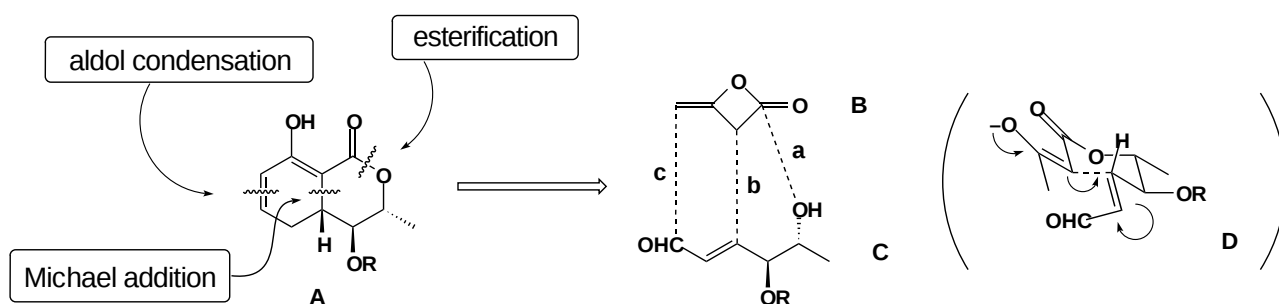


Figure 1.

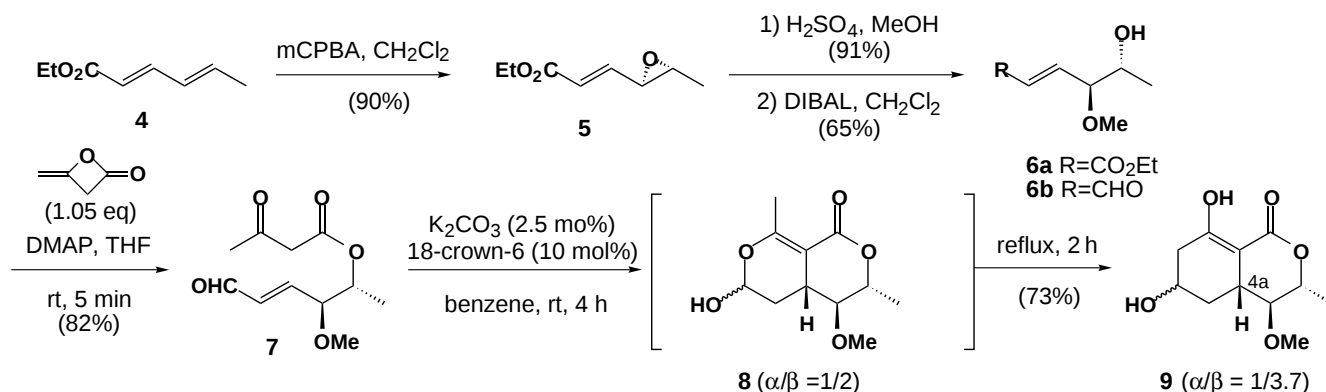
Our synthetic strategy is shown in Scheme 1. The target skeleton (**A**) was thought to be made from two moiety, diketene (**B**) and δ -hydroxy- α,β -unsaturated aldehyde (**C**) by esterification (**a**) at first, then Michael addition (**b**) of enolate generated by opening the diketene β -lactone,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

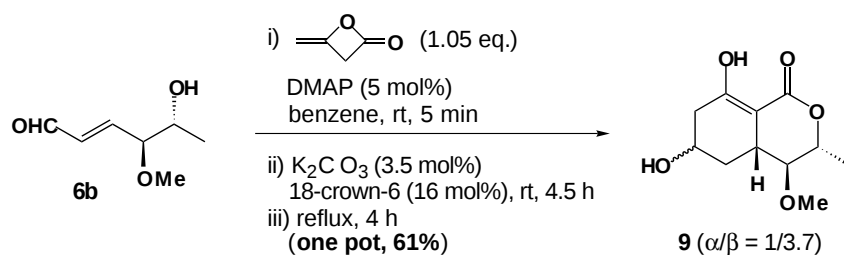
axial direction because of a favored conformation of the transition state (**D**) (the conformation of the six-membered ring refers chair form with substituents all equatorial).

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)pyridine⁷ 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.

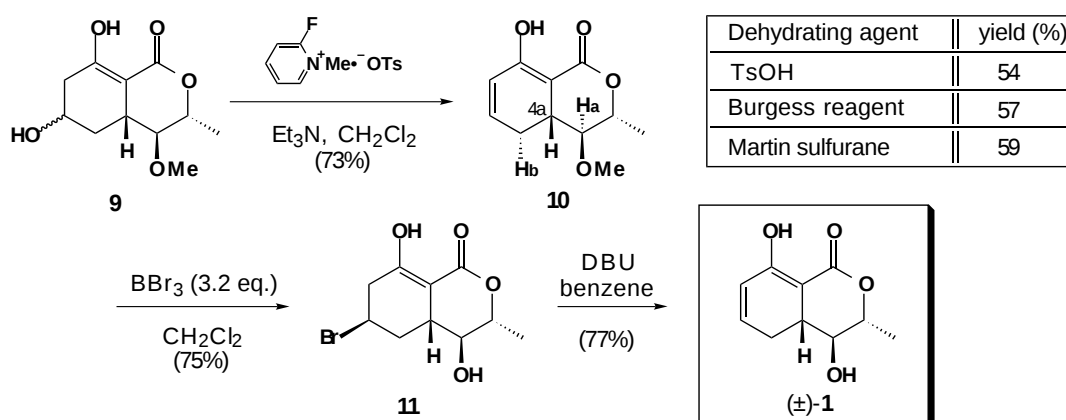
We then tried the one-pot esterification–Michael addition–aldol reaction from **6b** to **9**. The best result is shown in Scheme 3. Using 1.05 equivalents of diketene, esterification proceeded smoothly in benzene. Then the addition of a catalytic amount of potassium carbonate and 18-crown-6 and heating 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 ¹H-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 reagent¹² (in benzene, reflux, 2 h) or Martin sulfurane¹³ (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 tosylate¹⁴ 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 H_a, 17.0 Hz with H_b). 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 ¹H- and ¹³C-NMR spectra were identical with those of natural **1**.^{1, 15}



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

We are much grateful to Professor John A. Findlay, Department of Chemistry, University of New Brunswick, for a kind gift of copies of IR, ¹H-NMR and ¹³C-NMR spectra of natural **1**.

REFERENCES AND NOTES

1. J. A. Findlay, S. Buthelezi, R. Lavoie, and L. Peña-Rodriguez, *J. Nat. Prod.*, 1995, **58**, 1759.
2. S. W. Tanenbaum, S. C. Agarwal, T. Williams, and R. G. Pitcher, *Tetrahedron Lett.*, 1970, 2377.
3. M. Devys, M. Barbier, J.-F. Bousquet, and A. Kollmann, *Z. Naturforsch.*, 1992, **47c**, 779.
4. (a) H. Nishikawa, *Nippon Nogeikagaku Kaishi (J. Agric. Chem. Soc. Jpn.)*, 1933, **9**, 772.
(b) T. Yabuta and Y. Sumiki, *Nippon Nogeikagaku Kaishi (J. Agric. Chem. Soc. Jpn.)*, 1933, **9**, 1264.
(c) J. F. Grove and M. Pople, *J. Chem. Soc., Perkin Trans. I*, 1979, 2048.
(d) M. Sasaki, Y. Kaneko, K. Oshita, H. Takamatsu, Y. Asao, and T. Yokotsuka, *Agric. Biol. Chem.*, 1970, **34**, 1296.
(e) D. C. Aldridge, S. Galt, D. Giles, and W. B. Turner, *J. Chem. Soc. (C)*, 1971, 1623.
(f) R. Nishida, T. C. Baker, W. L. Roelofs, and T. E. Acree, *Abstracts of Papers*, Pest 100, 186th A.C.S. National Meeting, Washington, D.C., August 28-September 2, 1983.
5. (a) F. H. Stodola, C. Cabot, and C. R. Benjamin, *Biochem. J.*, 1964, **93**, 92.
(b) J. A. Findlay, J. M. Matsoukas, and J. Krepinsky, *Can. J. Chem.*, 1976, **54**, 3419.
6. (a) W. B. Turner and D. C. Aldridge, 'Fungal Metabolites', Academic Press, London, 1983, pp. 82-109.
(b) R. F. Struck, M. C. Thorpe, W. C. Coburn, Jr., and Y. F. Shealy, *Tetrahedron Lett.*, 1967, 1589.
7. A. Nudelman, R. Kelner, N. Broida, and H. E. Gottlieb, *Synthesis*, 1989, 387.
8. G. V. Kryshnal, V. V. Kulganek, V. F. Kucherov, and L. A. Yanovskaya, *Synthesis*, 1979, 107.
9. K. M. Pietrusiewicz and J. Monkiewicz, *J. Org. Chem.*, 1983, **48**, 788.
10. J. A. Elix and J. H. Wardlaw, *Aust. J. Chem.*, 1996, **48**, 917.
11. W. L. Meyer, C. W. Sigel, R. J. Hoff, T. E. Goodwin, R. A. Manning, and P. G. Schroeder, *J. Org. Chem.*, 1977, **42**, 4131.
12. (a) E. M. Burgess, H. R. Penton, Jr., and E. A. Taylor, *J. Am. Chem. Soc.*, 1970, **92**, 5224.
(b) E. M. Burgess, H. R. Penton, Jr., and E. A. Taylor, *J. Org. Chem.*, 1973, **38**, 26.
13. (a) J. C. Martin and R. J. Arhart, *J. Am. Chem. Soc.*, 1971, **93**, 2341.
(b) R. J. Arhart and J. C. Martin, *J. Am. Chem. Soc.*, 1972, **94**, 5003.
14. T. Mukaiyama, *Angew. Chem., Int. Ed. Engl.*, 1979, **18**, 707.
15. The spectral data of synthetic ($\pm$)-**1** are shown below. IR (KBr): ν = 3400, 2840, 1650, 1610, 1580, 1410, 1390, 1370, 1345, 1310, 1240, 1190, 1065 cm^{-1} ; ¹H-NMR (500 MHz in CDCl₃): 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, 3.0 Hz, 7-H), 6.51 (1H, ddd, J = 9.8 Hz, 6.3 Hz, 2.2 Hz, 6-H), 12.81 (1H, s, 8-OH); ¹³C-NMR (125 MHz in CDCl₃): δ = 17.8, 27.6, 37.5, 74.4, 78.1, 90.5, 124.4, 140.3, 169.2, 170.9.
16. M. Frohn, M. Dalkiewicz, Y. Tu, Z.-X. Wang, and Y. Shi, *J. Org. Chem.*, 1998, **63**, 2948.