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Total Synthesis of (−)- and (±)-Frontalin *via* Ring-Closing Metathesis

Matthias Scholl and Robert H. Grubbs*

The Arnold and Mabel Beckman Laboratory of Chemical Synthesis, Division of Chemistry and Chemical Engineering, California Institute of Technology, Pasadena, CA 91125

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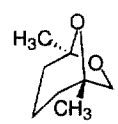
Abstract: Racemic and enantiopure targets containing the 6,8-dioxabicyclo [3.2.1]octane skeleton, can be conveniently synthesized from monocyclic diene precursors using an intramolecular ruthenium-catalyzed ring-closing metathesis reaction as the key step.

Ring-closing metathesis (RCM), catalyzed by transition metal carbenes, has recently become a popular tool for the conversion of acyclic dienes to cycloolefins.[1] While a large number of mono- and polycyclic compounds has been prepared by this method, not much effort has been directed toward application of RCM to the construction of bridged systems, so ubiquitous in natural products. A recent report from this laboratory described the first application of RCM to the formation of small ring bridged bicycloalkenes from monocyclic dienes.[2] We now report the first synthesis of small ring bridged oxygen heterocycles using RCM as demonstrated by the synthesis of **1**.



1

The 6,8-dioxabicyclo[3.2.1]octane ring system defines the skeleton of frontalin (**1**), the aggregation pheromone of the southern bark beetle *Dendroctonus frontalis*.[3] Although the biologically active enantiomer of frontalin (1*S*,5*R*)[4] contains two chiral centers, only one of them needs to be considered since the correct configuration of the second center is dictated by the formation of the bicyclic structure. The 1*S* center can be set in the 1,2-diol **2** with a high

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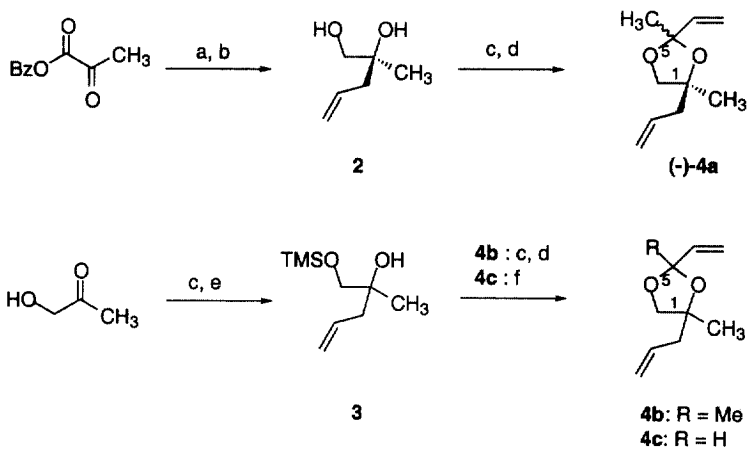
degree of enantiocontrol, utilizing either the recently developed Mukiyama asymmetric allylation[5] or the Sharpless asymmetric dihydroxylation[6] reaction (Scheme 1).[7] Alternatively, the racemic mono-TMS-protected 1,2-diol **3** can be conveniently prepared *via* Grignard addition of allyl magnesium chloride to the TMS-protected hydroxyacetone.

Scheme 1

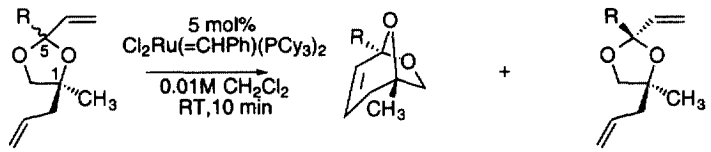


a: Sn(II)-catecholate, (+)-DIPT, DBU, CuI, Allyl-Br, CH_2Cl_2, -78°C, 81%; b: $LiAlH_4$, Et_2O, 0°C, then 25°C, 89%; c: TMS-Cl, Et_3N, CH_2Cl_2, 0°C, then 25°C, 83%; d: MVK, cat. TMS-OTf, CH_2Cl_2, -78°C, then -20°C, 85%; e: H_2C=$CHCH_2MgCl$, THF, 0°C, 67%; f: H_2C=$CHCH(OCH_3)_2$, cat. CH_3COCl, CH_2Cl_2, 0°C, 74%.

To utilize RCM for the formation of the bicyclic structures, the monocyclic dienes **4a**[8] and **4b-c** are prepared starting from enantiopure[9] (**2**) and reacemic (**3**) diols, respectively. The ketals **4a** and **4b** are synthesized under mild conditions using Noyori's TMS-OTf assisted ketal formation[10] and the acetal **4c** is prepared via acetyl chloride-catalyzed condensation of **3** with acrolein dimethyl acetal.

Formation of bicyclo[3.2.1]alkenes by closure of the six membered ring is extremely facile.[2] The ring closed products **5a-c** can be obtained within minutes at room temperature by treatment of **4a-c** with a catalytic amount of ruthenium benzylidene[11] (Scheme 2). Since the precursors **4a-c** are most conveniently prepared as a mixture of the *syn*- and *anti*-isomers and only the *syn*-isomer can undergo cyclization, the unreacted *anti*-isomers **4a'-c'** can be recovered[12] and are easily equilibrated to a mixture of the two isomers.[13]

Scheme 2



(-)-4a : (1-*S*), R = Me
4b : R = Me
4c : R = H

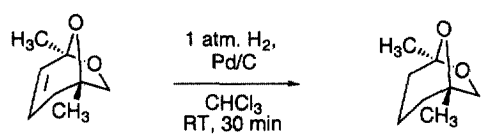
(-)-5a : (1-*S*) (5-*R*), R = Me (89%)[a]
5b : R = Me (89%)
5c : R = H (90%)

(+)-4a' : (1-*S*) (5-*S*), R = Me (89%)[a]
4b' : R = Me (89%)
4c' : R = H (90%)

[a] yields based on the amount of *syn*- and *anti*-diastereomers of **4**, respectively

Finally, the 1,5-dimethyl-6,8-dioxabicylo[3.2.1]oct-3-enes **5a** and **5b** are hydrogenated to yield racemic and enantiopure frontalin **1a** and **1b**, respectively, in excellent yields[14] (Scheme 3). Synthetic **1a** shows nearly identical optical rotation to that reported for the authentic (-)-isomer ($[\alpha]_D$ -50.0 vs lit.[4] $[\alpha]_D$ –52.0).

Scheme 3



(-)-5a
(±)-5b

(-)-1a : (89%)
(±)-1b : (89%)

In conclusion, enantiopure and racemic products, such as frontalin, containing the 6,8-dioxabicyclo[3.2.1]octane skeleton can be prepared in 4 steps from 2-methyl-4-pentene-1,2-diols **2** and **3**, respectively. Current investigations are directed at *in situ* epimerization[15] of the C5 center of the monocyclic acetals and ketals **4a-c** leading to a theoretically quantitative conversion of **4a-c** to the corresponding bicycles **5a-c**. In addition, the synthesis of other small ring bridged natural products *via* RCM is in progress.

Acknowledgements.

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8. Characterization data: **1a** and **1b**: match lit.: Whitesell, J. K.; Buchanan, C. M. *J. Org. Chem.* **1986**, *51*, 5443-5445.; **1a**: $[\alpha]_D$ -50.0°; **2**: NMR and IR match lit.: Barluenga, J.; Florez, J.; Yus, M. *J. Chem. Soc. - Perkin Trans. 1* **1983**, 3019-3026.; HRMS calcd for $C_6H_{16}NO_2$ (MNH_4^+) 134.1181, found 134.1188; **4a** and **4b** (each ~1:1 mixture of *syn*- and *anti*-diastereomers): ^{1}H NMR ($CDCl_3$, 400 MHz) δ 5.86-5.71 (m, 4H), 5.38-5.32 (m, 2H), 5.10-5.02 (m, 6H), 3.80 (d, *J* = 8.4 Hz, 1H), 3.72 (d, *J* = 8 Hz, 1H), 3.69 (d, *J* = 8.0 Hz, 1H), 3.53 (d, *J* = 8.4 Hz, 1H), 2.39-2.23 (m, 4H), 1.45 (s, 6H), 1.28 (s, 3H), 1.26 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 140.0, 140.0, 133.9, 133.8, 118.3, 118.2, 114.4, 114.3, 108.2, 108.1, 81.2, 81.2, 73.9, 73.2, 45.0, 44.0, 26.2, 26.2, 25.0, 23.9; IR (neat, cm^{-1}) 2968, 1630, 1426, 1374, 1218, 1166, 1047; HRMS calcd for $C_{10}H_{17}O_2$ (MH^+) 169.1229, found 169.1228; **4a'**and **4b'**: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 5.89-5.79 (m, 2H), 5.38-5.32 (m, 1H), 5.12-5.09 (m, 3H), 3.80 (d, *J* = 8.4 Hz, 1H), 3.53 (d, *J* = 8.4 Hz, 1H), 2.35-2.26 (m, 2H), 1.45 (s, 3H), 1.28 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 140.0, 134.0, 118.3, 114.4, 108.2, 81.3, 73.3, 45.0, 26.2, 23.9; IR (neat, cm^{-1}) 2931, 1641, 1372, 1217, 1170, 1050; HRMS calcd for $C_{10}H_{17}O_2$ (MH^+) 169.1229, found 169.1228; **4c**: (~1:1 mixture of *syn*- and *anti*-diastereomers): ^{1}H NMR ($CDCl_3$, 400 MHz) δ : 5.86-5.75 (m, 4H), 5.50-5.43 (m, 2H), 5.35-5.29 (m, 4H), 5.14-5.07 (m, 4H), 3.85 (d, *J* = 7.6 Hz, 1H), 3.74 (d, *J* = 7.6 Hz, 1H), 3.66 (d, *J* = 7.6 Hz, 1H), 3.55 (d, *J* = 7.6 Hz, 1H), 2.42-2.30 (m, 4H), 1.29 (s, 3H), 1.29 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 135.4, 135.1, 133.6, 133.4, 120.1, 119.9, 118.5, 118.4, 104.0, 103.5, 80.8, 80.7, 74.4, 44.5, 43.1, 30.4, 24.7, 23.3; IR (neat, cm^{-1}) 2978, 1642, 1436, 1377, 1097; HRMS calcd for $C_9H_{15}O_2$ (MH^+) 155.1072, found 155.1070; **4c'**: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 5.84-5.72 (m, 2H), 5.41 (d, *J* = 17.2 Hz, 1H), 5.31-5.26 (m, 2H), 5.09-5.04 (m, 2H), 3.70 (d, *J* = 8.0 Hz, 1H), 3.62 (d, *J* = 8.0 Hz, 1H), 2.39-2.25 (m, 2H), 1.26 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 135.4, 133.4, 119.9, 118.5, 104.0, 80.8, 74.4, 43.1, 24.7; IR (neat, cm^{-1}) 2979, 1728, 1642, 1436, 1378, 1097; HRMS calcd for $C_9H_{15}O_2$ (MH^+) 155.1072, found 155.1070; **5a** and **5b**: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 5.80-5.66 (m, 2H), 3.72 (d, *J* = 7.3 Hz, 1H), 3.53-3.50 (m, 1H), 2.40 (dd, *J* = 17.9, 7.3, 1H), 1.99-1.93 (m, 1H), 1.51 (s, 3H), 1.41 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 131.0, 125.3, 103.3, 78.9, 74.6, 38.6, 24.1, 22.1; IR (neat, cm^{-1}) 2932, 1711, 1374, 1260, 1062, 1020; HRMS calcd for $C_8H_{12}O_2$ (M^+) 140.0837, found 140.0846; **5c**: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 5.85-5.81 (m, 1H), 5.72-5.67 (m, 1H), 5.44 (d, *J* = 3.3 Hz, 1H), 3.72 (d, *J* = 7.3 Hz, 1H), 3.42 (dd, *J* = 7.3, 3.3 Hz, 1H), 2.48-2.41 (m, 1H), 2.00-1.94 (m, 1H), 1.39 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 128.0, 126.1, 97.3, 77.8, 73.5, 39.3, 23.8; IR (neat, cm^{-1}) 2973, 1686, 1638, 1384, 1169, 1073; HRMS calcd for $C_7H_{10}O_2$ (M^+) 126.0681, found 126.0689.
9. The enantiopurity of the 2-hydroxy-2-methyl-pent-4-enoic acid benzyl ester derived from the Mukaiyama allylation reaction is assessed to be 99+% as determined by its optical rotation ($[\alpha]_D$ 6.5 vs lit.[5] $[\alpha]_D$ 5.8) and the ^{1}H NMR analysis of its Moscher's ester. The absolute configuration of the 2-hydroxy-2-methyl-pent-4-enoic acid benzyl ester was determined to be (*S*) by the conversion to (*S*)-(+)-dimethyl citramalate.[5]
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12. No dimerization of the non-cyclizable isomer of (+)-4a was observed at 0.01M; the reaction was not run at any other concentrations.
13 Treatment of the *anti*-isomer with a cat. amount of Amberlyst® 15 acidic ion exchange resin results in a rapid equilibration to a mixture of the *syn*- and *anti*-isomers.
14. Yields determined by ^{1}H NMR are quantitative; isolated yields are slightly lower due to high volatility of products.
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