

Tetrahedron Letters 40 (1999) 1425-1428

TETRAHEDRON LETTERS

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

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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. © 1999 Elsevier Science Ltd. All rights reserved.

Ring-closing metathesis (RCM), catalyzed by transition metal carbenes, has recently become a popular tool for the conversion of acyclic dienes to cycloolefins.<sup>1</sup> 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.<sup>2</sup> We now report the first synthesis of small ring bridged oxygen heterocycles using RCM as demonstrated by the synthesis of 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.*<sup>3</sup> Although the biologically active enantiomer of frontalin  $(1S,5R)^4$  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 1S center can be set in the 1,2-diol 2 with a high

degree of enantiocontrol, utilizing either the recently developed Mukiyama asymmetric allylation<sup>5</sup> or the Sharpless asymmetric dihydroxylation<sup>6</sup> reaction (Scheme 1).<sup>7</sup> 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, Cul, AllyI-Br, CH<sub>2</sub>Cl<sub>2</sub>, -78°C, 81%; b: LiAlH<sub>4</sub>, Et<sub>2</sub>O, 0°C, then 25°C, 89%; c: TMS-CI, Et<sub>3</sub>N, CH<sub>2</sub>Cl<sub>2</sub>, 0°C, then 25°C, 83%; d: MVK, cat. TMS-OTf, CH<sub>2</sub>Cl<sub>2</sub>, -78°C, then -20°C, 85%; e: H<sub>2</sub>C=CHCH<sub>2</sub>MgCI, THF, 0°C, 67%; f: H<sub>2</sub>C=CHCH(OCH<sub>3</sub>)<sub>2</sub>, cat. CH<sub>3</sub>COCI, CH<sub>2</sub>Cl<sub>2</sub>, 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<sup>9</sup> (2) and reacemic (3) diols, respectively. The ketals 4a and 4b are synthesized under mild conditions using Noyori's TMS-OTf assisted ketal formation<sup>10</sup> 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.<sup>2</sup> 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<sup>11</sup> (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<sup>12</sup> and are easily equilibrated to a mixture of the two isomers.<sup>13</sup>



<sup>a</sup> 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<sup>14</sup> (Scheme 3). Synthetic **1a** shows nearly identical optical rotation to that reported for the authentic (-)-isomer ( $[\alpha]_D$  -50.0 vs lit.<sup>4</sup>  $[\alpha]_D$  -52.0).

#### Scheme 3



In conclusion, enantiopure and racemic products, such as frontalin, containing the 6,8dioxabicyclo[3.2.1]octane skeleton can be prepared in 4 steps from 2-methyl-4-pentene-1,2diols 2 and 3, respectively. Current investigations are directed at *in situ* epimerization<sup>15</sup> 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.

Support has been generously provided by the National Institutes of Health. MS thanks

Pharmacia and Upjohn for a Graduate Fellowship in Synthetic Organic Chemistry. The authors thank Dr. Andrew Morehead Jr. for useful discussions.

### **References and Notes.**

- 1. For recent reviews of RCM see: (a) Armstrong, S. K. J. Chem. Soc. - Perkin Trans. 1 1998, 371-388.; (b) Randall, M. L.; Snapper, M. L. J. Mol. Cat. A-Chem. 1998, 133, 29-40.; (c) Schuster, M.; Blechert, S. Angew. Chem., Int. Ed. Engl. 1997, 36, 2037-2056.; (d) Ivin, K. J. J. Mol. Cat. A-Chem. 1998, 133, 1-16.
- 2. Morehead, A.; Grubbs, R. Chem. Comm. 1998, 275-276.
- 3. For recent syntheses of frontalin see: (a) Nishimura, Y.; Mori, K. Eur. J. Org. Chem. 1998, 233-236.; (b) Majewski, M.; Nowak, P. Tetrahedron-Asymmetry 1998, 9, 2611-2617.; (c) Maezaki, N.; Shogaki, T.; Uchida, M.; Tokuno, K.; Imamura, T.; Tanaka, T.; Iwata, C. Chem. Pharm. Bull. 1998, 46, 217-221. Mori, K. Tetrahedron 1975, 31, 1381-1384.
- 4.
- Yamada, K.; Tozawa, T.; Nishida, M.; Mukaiyama, T. Bull. Chem. Soc. Japan 1997, 70, 2301-2308. 5.
- Becker, H.; King, S. B.; Taniguchi, M.; Vanhessche, K. P. M.; Sharpless, K. B. J. Org. Chem. 1995, 60, 3940-6. 3941.
- 7. For a similar approach to define the 1S stereocenter see: Turpin, J. A.; Weigel, L. O. Tet. Lett. 1992, 33, 6563-6564.
- 6563-6564. 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<sub>6</sub>H<sub>1p</sub>NO<sub>2</sub> (MNH<sub>4</sub><sup>+</sup>) 134.1181, found 134.1188; **4a** and **4b** (each ~1:1 mixture of syn- and anti-diastereomers): <sup>1</sup>H NMR (CDCl<sub>3</sub>, 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); <sup>13</sup>C NMR (CDCl<sub>3</sub>, 100 MHz) δ 140.0, 140.0, 133.9, 133.8, 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<sup>-1</sup>) 2968, 1630, 1426, 1374, 1218, 1166, 1047; HRMS calcd for C<sub>10</sub>H<sub>17</sub>O<sub>2</sub> (MH<sup>+</sup>) 169.1229, found 169.1228; **4a**'and **4b**': <sup>1</sup>H NMR (CDCl<sub>3</sub>, 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). 8. 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); <sup>13</sup>C NMR (CDCl<sub>3</sub>, 100 MHz)  $\delta$  140.0, 134.0, 118.3, 114.4, 108.2, 81.3, 73.3, 45.0, 26.2, 23.9; IR (neat, cm<sup>-1</sup>) 2931, 1641, 1372, 1217, 1170, 1050; HRMS calcd for  $C_{10}H_{17}O_2$  (MH<sup>+</sup>) 169.1229, found 169.1228; 4c: (~1:1 mixture of syn- and anti-diastereomers): <sup>1</sup>H NMR (CDCl<sub>3</sub>, 400 MHz)  $\delta$  : 5.86found 169.1228; 4c: (~1:1 mixture of syn- and anti-diastereomers): <sup>1</sup>H NMR (CDCl<sub>3</sub>, 400 MHz)  $\delta$  : 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); <sup>13</sup>C NMR (CDCl<sub>3</sub>, 100 MHz)  $\delta$  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<sup>-1</sup>) 2978, 1642, 1436, 1377, 1097; HRMS calcd for C<sub>9</sub>H<sub>15</sub>O<sub>2</sub> (MH<sup>+</sup>) 155.1072, found 155.1070; 4c<sup>+</sup>: <sup>1</sup>H NMR (CDCl<sub>3</sub>, 400 MHz)  $\delta$  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); <sup>13</sup>C NMR (CDCl<sub>3</sub>, 100 MHz)  $\delta$  135.4, 133.4, 119.9, 118.5, 104.0, 80.8, 74.4, 43.1, 24.7; IR (neat, cm<sup>-1</sup>) 2979, 1728, 1642, 1436, 1378, 1097; HRMS calcd for C<sub>9</sub>H<sub>15</sub>O<sub>2</sub> (MH<sup>+</sup>) 155.1072, found 155.1070; dot MHz)  $\delta$  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); <sup>13</sup>C NMR (CDCl<sub>3</sub>, 100 MHz)  $\delta$  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); <sup>13</sup>C NMR (CDCl<sub>3</sub>, 100 MHz)  $\delta$  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); <sup>13</sup>C NMR (CDCl<sub>3</sub>, 100 MHz)  $\delta$  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); <sup>13</sup>C NMR (CDCl<sub>3</sub>, 100 MHz)  $\delta$  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); <sup>13</sup>C NMR (CDCl<sub>3</sub>, 100 MHz)  $\delta$  131.0, 125.3, 103.3, 78.9, 74.6, 38.6, 24.1, 22.1; IR (neat, cm<sup>-1</sup>) 2932, 1711, 1374, 1260, 1062, 110.8 18) MHz) § 131.0, 125.3, 103.3, 78.9, 74.6, 38.6, 24.1, 22.1; IR (neat, cm<sup>-1</sup>) 2932, 1711, 1374, 1260, 1062, 1020; HRMS calcd for  $C_8H_{12}O_2$  (M<sup>+</sup>) 140.0837, found 140.0846; Se: <sup>1</sup>H NMR (CDCl<sub>3</sub>, 400 MHz)  $\delta$  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); <sup>13</sup>C NMR (CDCl<sub>3</sub>, 100 MHz)  $\delta$  128.0, 126.1, 97.3, 77.8, 73.5, 39.3, 23.8; IR (neat, cm<sup>-1</sup>) 2973, 1686, 1638, 1384, 1169, 1073; HRMS calcd for  $C_7H_{10}O_2$  (M<sup>+</sup>) 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 ( $[\alpha]_p$  6.5 vs lit.<sup>5</sup>  $[\alpha]_p$  5.8) and the <sup>1</sup>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.
- 10. Tsunoda, T.; Suzuki, M.; Noyori, R. Tet. Lett. 1980, 21, 1357-1358.
- (a) Schwab, P.; France, M. B.; Ziller, J. W.; Grubbs, R. H. Angew. Chem., Int. Ed. Engl. 1995, 34, 2039-2041.; (b) Schwab, P.; Grubbs, R. H.; Ziller, J. W. J. Am. Chem. Soc. 1996, 118, 100-110. 11.
- No dimerization of the non-cyclizable isomer of (+)-4a was observed at 0.01M; the reaction was not run at 12. any other concentrations.
- 13 Treatment of the anti-isomer with a cat. amount of Amberlyst<sup>®</sup> 15 acidic ion exchange resin results in a rapid equilibration to a mixture of the syn- and anti-isomers.
- 14. Yields determined by 'H NMR are quantitative; isolated yields are slightly lower due to high volatility of products.
- Gassman, P. G.; Singleton, D. A.; Wilwerding, J. J.; Chavan, S. P. J. Am. Chem. Soc. 1987, 109, 2182-2184. 15.