ORGANIC LETTERS

1999
Vol. 1, No. 11
1827−1829

Desymmetrization by Ring-Closing Metathesis Leading to 6,8-Dioxabicyclo[3.2.1]octanes: A New Route for the Synthesis of (+)-*exo*- and *endo*-Brevicomin

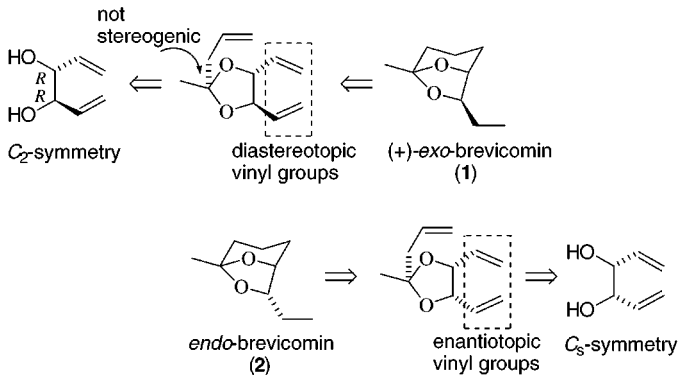
Steven D. Burke,* Norbert Müller, and Christopher M. Beaudry

Department of Chemistry, University of Wisconsin−Madison, 1101 University Avenue, Madison, Wisconsin 53706-1396

burke@chem.wisc.edu

Received September 28, 1999

ABSTRACT



The 6,8-dioxabicyclo[3.2.1]octane skeleton is a common structural subunit in natural products. A conceptionally new strategy affording these structures is described for the syntheses of (+)-*exo*-brevicomin and *rac*-*endo*- and enantiomerically enriched (+)-*endo*-brevicomin, employing desymmetrization of trienes derived from diols with C_2 and meso symmetry via ring-closing metathesis.

Ring-closing metathesis[1] has recently been featured in novel constructions of small,[2] medium,[3] and large[4] rings. Enantioselective ring-closing metatheses are also emerging.[5] Reconsideration, at the strategic level, of synthetic approaches

(1) For recent reviews, see: (a) Schrock, R. R. *Tetrahedron* **1999**, *55*, 8141−8153. (b) Grubbs, R. H.; Chang, S. *Tetrahedron* **1998**, *54*, 4413−4450. (c) Armstrong, S. K. *J. Chem. Soc., Perkin Trans. 1* **1998**, 371−388. Schuster, M.; Blechert, S. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 2037−2056.

(2) For recent examples, see: (a) Maier, M. E.; Bugl, M. *Synlett* **1998**, *12*, 1390−1392. (b) Burke, S. D.; Quinn, K. J.; Chen, V. J. *J. Org. Chem.* **1998**, *63*, 8626−8627. (c) Tanner, D.; Hagberg, L.; Poulsen, A. *Tetrahedron* **1999**, *55*, 1427−1440.

(3) For recent examples, see: (a) Delgado, M.; Martin, J. D. *J. Org. Chem.* **1999**, *64*, 4798−4816. (b) Gerlach, K.; Quitschalle, M.; Kalesse, M. *Tetrahedron Lett.* **1999**, *40*, 3553−3556. (c) Schneider, M. V.; Junga, H.; Blechert, S. *Tetrahedron* **1995**, *51*, 13003−13014. (d) Miller, S. J.; Kim, S.-K.; Chen, Z.-R.; Grubbs, R. H. *J. Am. Chem. Soc.* **1995**, *117*, 2108−2109.

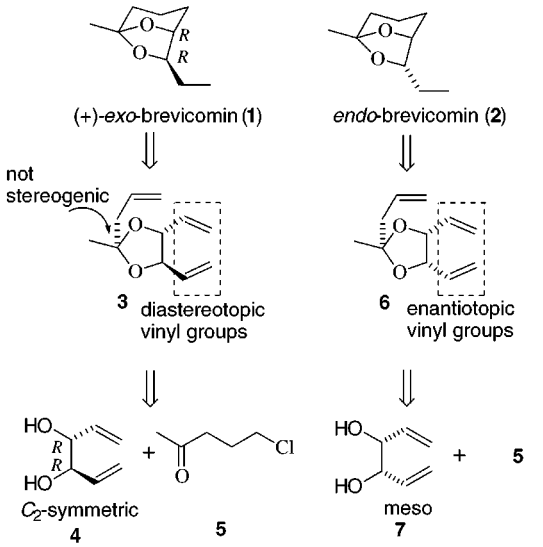
(4) For recent examples, see: (a) Martin Cabrejas, L. M.; Rohrbach, S.; Wagner, D.; Kallen, J.; Zenke, G.; Wagner, J. *Angew. Chem., Int. Ed. Engl.* **1999**, *38*, 2443−2446. (b) Weck, M.; Mohr, B.; Sauvage, J.-P.; Grubbs, R. H. *J. Org. Chem.* **1999**, *15*, 5463−5471. (c) Schinzer, D.; Limberg, A.; Bauer, A.; Böhm, O. M.; Cordes, M. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 523−524. (d) Fürstner, A.; Müller, T. *J. Am. Chem. Soc.* **1999**, *121*, 7814−7821.

(5) (a) Zhu, S. S.; Cefalo, D. R.; La, D. S.; Jamieson, J. Y.; Davis, W. M.; Hoveyda, A. H.; Schrock, R. R. *J. Am. Chem. Soc.* **1999**, *121*, 8251−8259. (b) La, D. S.; Alexander, J. B.; Cefalo, D. R.; Graf, D. D.; Hoveyda, A. H.; Schrock, R. R. *J. Am. Chem. Soc.* **1998**, *120*, 9720−9721. Alexander, J. B.; La, D. S.; Cefalo, D. R.; Hoveyda, A. H.; Schrock, R. R. *J. Am. Chem. Soc.* **1998**, *120*, 4041−4042. (c) Fujimura, O.; Grubbs, R. H. *J. Am. Chem. Soc.* **1996**, *118*, 2499−2500. (d) Fujimura, O.; Grubbs, R. H. *J. Org. Chem.* **1998**, *63*, 824−832.

10.1021/ol9910971 CCC: $18.00
Published on Web 10/22/1999

to common structural motifs has been stimulated by this powerful cycloalkene-forming method. Consider, for example, the 6,8-dioxabicyclo[3.2.1]octane nucleus present as a structural element in complex natural products such as palytoxin[6] and pinnatoxin D,[7] and in simpler insect pheromones such as *exo*- and *endo*-brevicomin (**1** and **2**, Scheme 1).[8] Synthetic routes to these bicyclic acetal units have

Scheme 1. Retrosynthetic Analysis



typically culminated in intramolecular ketodiol-to-acetal dehydration, following subunit convergence by intermolecular C−C bond formation. A strategy employing intermolecular acetalization for subunit convergence and *intramolecular* C−C bond formation has obvious appeal, but has gone largely unexplored.[9,10]

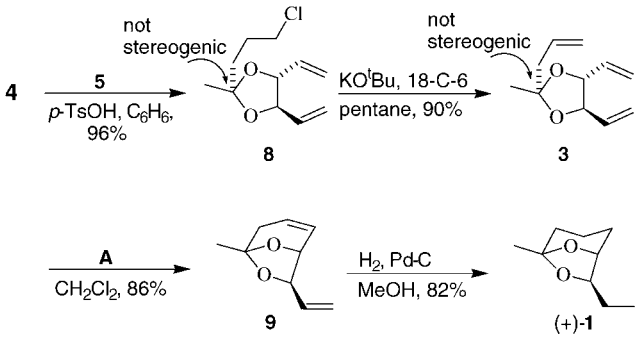
Described herein is a demonstration of this strategy for very short syntheses of (+)-*exo*-, *rac*-*endo*-, and enantiomerically enriched (+)-*endo*-brevicomin (**1** and **2**), employing catalytic ring-closing metathesis for carbocycle formation[10] and substrate desymmetrization. These simple and stereoselective insect pheromone syntheses are amenable to scale-up and could be suitable for industrial application. Initial results from the use of a chiral metathesis catalyst for enantioselective desymmetrization of a meso substrate to yield (+)-*endo*-brevicomin are also presented.

The *exo*- and *endo*-isomers of brevicomin (**1** and **2**, respectively) are constituents of volatiles from several species of bark beetles and have been shown to be necessary for their communication. (+)-*exo*-Brevicomin (**1**) is the aggregation pheromone of the western pine beetle, *Dendroctonus brevicomis*.[11] (+)-*endo*-Brevicomin enhances the response of southern pine beetles, *Dendroctonus frontalis*, to the female-produced pheromone frontalin, and (−)-*endo*-brevicomin significantly reduces this response.[12] Because of the serious damage these insects can cause in pine forests,[13] the pheromones are commercially used in their control. Synthesis of these compounds has been intensively studied.[8b,9a−c,14]

The retrosynthetic analysis (Scheme 1) for (+)-*exo*-brevicomin (**1**) employs C−C bond disconnection in the six-membered carbocyclic ring of the bicyclic acetal, resulting in triene **3**. Metathesis substrate **3** derives from intermolecular ketalization between (3*R*,4*R*)-3,4-dihydroxy-1,5-hexadiene (**4**)[15] and ketone **5**. For *endo*-brevicomin (**2**), ketal **6** emerges as the metathesis substrate, arising from meso diol **7** and ketone **5**.

Ketalization of commercially available 5-chloro-2-pentanone (**5**) with diol **4** under Dean−Stark conditions gave the ketal **8** in 96% yield (Scheme 2). Elimination with KO^{t}Bu

Scheme 2. Synthesis of (+)-*exo*-Brevicomin



and a catalytic amount of 18-crown-6 afforded the desired triene **3** together with its internal double bond isomer in an inseparable 14:1 mixture (90%). Ring-closing metathesis with 2 mol % of the Grubbs catalyst A (Figure 1) converted **3** in

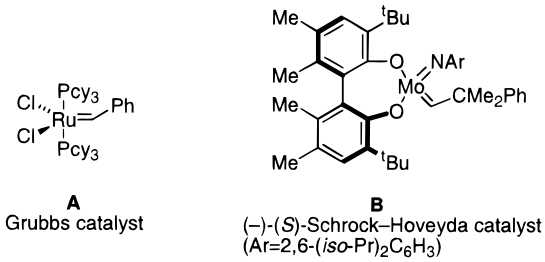


Figure 1.

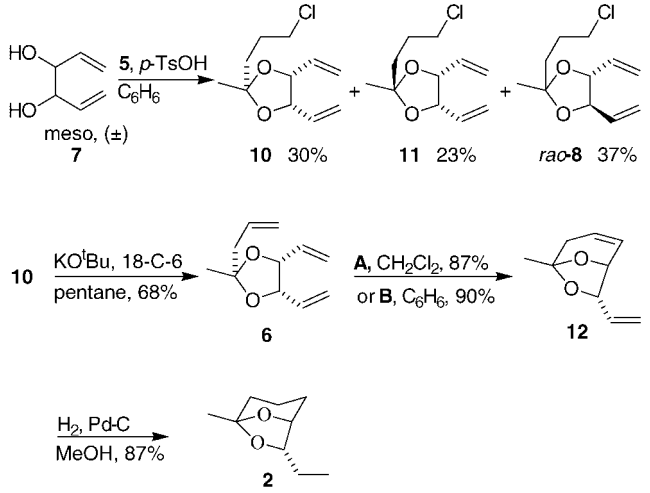
high yield (86%) to the 6,8-dioxabicyclo[3.2.1]octane skeleton **9**, for which an X-ray crystal structure was obtained. The minor internal double bond isomer did not react and was separated by flash chromatography. Catalytic hydrogen-

(6) Moore, R. E. *Prog. Chem. Org. Nat. Prod.* **1985**, *48*, 81−202.
(7) Chou, T.; Haino, T.; Kuramoto, M.; Uemura, D. *Tetrahedron Lett.* **1996**, 37, 4023−4026.
(8) (a) Silverstein, R. M.; Brownlee, R. G.; Bellas, T. E.; Wood, D. L.; Browne, L. E. *Science* **1968**, *159*, 889−891. (b) Mori, K. *Tetrahedron* **1989**, *45*, 3233−3298 and references therein.
(9) (a) Meister, C.; Shen, Z.; Scharf, H.-D. *Liebigs Ann. Chem.* **1984**, 147−156. (b) Gypser, A.; Flasche, M.; Scharf , H.-D. *Liebigs Ann. Chem.* **1994**, 775−780. (c) Wershofen, S.; Classen, A.; Scharf, H.-D. *Liebigs Ann. Chem.* **1989**, 9−18.

ation of **9** afforded (+)-*exo*-brevicomin (**1**) (82%).[16] The observed optical rotation of **1**, $[\alpha]^{23}_D = +71.5°$ ($c = 1.03$ in Et_2O) is consistent with those reported in the literature for samples with known enantiomeric excess: $[\alpha]^{20}_D = +72.4°$, ee = 99.8%, ($c = 2.0$ in Et_2O);[17] $[\alpha]^{23}_D = +69.3°$($c = 2.5$ in Et_2O), ee > 99%.[18] (−)-*exo*-Brevicomin should also be available from (3*S*,4*S*)-3,4-dihydroxy-1,5-hexadiene via this sequence.[19]

A racemic synthesis of *endo*-brevicomin (**2**) (Scheme 3) proceeded similarly. In this case, the starting material is a

Scheme 3. Synthesis of *endo*-Brevicomin



commercially available mixture of meso and (±) diols **7**, which can also be prepared from a pinacol reduction of acrolein.[20] Although selective multistep syntheses of the pure meso diol **7** are known,[19,21] we employed the readily available mixture. Ketalization of 5-chloro-2-pentanone (**5**) with a 1.55:1 meso,(±) mixture of **7** afforded the three diastereomers *meso*-**10** (30%), *meso*-**11** (23%), and *rac*-**8** (37%), which were separated by flash column chromatography. Subjection of the meso,cis ketal **10** to the elimination conditions produced **6** together with small amounts of its internal double bond isomer (45:1, 68%). The meso triene **6** was desymmetrized to the racemic 6,8-dioxabicyclo[3.2.1]-octane skeleton **12** (87%), with the vinyl group endo, via ring-closing metathesis using 7 mol % of the Grubbs catalyst A (Figure 1). As before, the internal double bond isomer of **6** did not react. Catalytic hydrogenation of **12** afforded racemic *endo*-brevicomin (**2**) (87%).[22]

The chiral, commercially available (−)-(*S*)-Schrock−Hoveyda catalyst B (Figure 1) was used for the asymmetric desymmetrization of the meso triene **6**. Ring-closing metathesis with 10 mol % of catalyst B afforded an enantioenriched mixture of (+)- and (−)-**12** with 55−59% ee (determined by chiral HPLC). The identity of the major enantiomer as (+)-**12** was established by comparison of the optical rotation of the hydrogenation product **2** ($[\alpha]^{22}_D = +37.5°$, $c = 1.00$ in Et_2O) with that of (+)-*endo*-brevicomin in the literature: $[\alpha]^{20}_D = +79.0°$ ($c = 1.10$ in Et_2O),[9b] $[\alpha]^{20}_D = +79.5°$ ($c = 1.18$ in Et_2O).[23]

In summary, a new strategy has been demonstrated for the stereoselective construction of the 6,8-dioxabicyclo[3.2.1]-octane skeletons of the brevicomins, based on desymmetrization of triene substrates via ring-closing metathesis. Initial results for the enantioselective desymmetrization of meso triene **6** have also been recorded. To our knowledge, this is the first time enantioselective ring-closing metathesis has been used in a natural product synthesis. The intermediate bicyclic acetals **9** and **12**, containing two double bonds, have substantial potential for further derivatization. Ongoing efforts will show that this strategy is also suitable for other bicyclic acetal structures.

Acknowledgment. We thank the Fonds der Chemischen Industrie, Germany (Ph.D. fellowship to N.M.), the Hilldale Scholarship Program (C.M.B.), the National Institutes of Health (Grant CA74394), and Abbott Laboratories for generous support. We are also grateful to Mr. Paul R. LePlae for his assistance with the HPLC analyses of **12** and Dr. Douglas R. Powell for X-ray crystallographic analysis of **9**.

OL9910971

(10) Frontalin, a structurally similar bicyclic acetal, was recently synthesized using ring-closing metathesis as the key step. The retrosynthetic strategy used for (−)-frontalin is distinguished from that which we employed for the brevicomins by a different C−C bond disconnection in the six-membered ring and introduction of the 1(*S*)-stereocenter via Mukiyama asymmetric allylation or Sharpless asymmetric dihydroxylation. See: Scholl, M.; Grubbs, R. H. *Tetrahedron Lett.* **1999**, *40*, 1425−1428.

(11) Wood, D. L.; Browne, L. E.; Ewing, B.; Bedard , W. D.; Tilden, P. E.; Mori, K.; Pitman, G. B.; Hughes, P. R. *Science* **1976**, *192*, 896−898.

(12) Vite, J. P.; Ware, C. W.; Billings, R. F.; Mori, K. *Naturwissenschaften* **1985**, *72*, 99−100.

(13) *U.S. Forest Insect and Disease Conditions in the U.S: 1985*; U.S.D.A. Forest Service Report, 1985.

(14) (a) Hu, S. J.; Jayaraman, S.; Oehlschlager, A. C. *J. Org. Chem.* **1999**, *64*, 2524−2526. (b) List, B.; Shabat, D.; Barbas, C. F.; Lerner, R. A. *Chem. Eur. J.* **1998**, *5*, 881−885. (c) Vettel, S.; Lutz, C.; Diefenbach, A.; Haderlein, G.; Hammerschmidt, S.; Kühling, K.; Mofid, M.-R.; Zimmermann, T.; Knochel, P. *Tetrahedron: Asymmetry* **1997**, *8*, 779−780.

(15) Burke, S. D.; Sametz, G. M. *Org. Lett.* **1999**, *1*, 72−74.

(16) Identical by comparison of ^1H and ^{13}C NMR data with those reported in ref 17.

(17) Mori, K.; Seu, Y.-B. *Liebigs Ann. Chem.* **1986**, 205−209.

(18) Mulzer, J.; Angermann, A.; Münch, W. *Liebigs Ann. Chem.* **1986**, 825−838.

(19) Kang, S. H.; Ryu, D. H. *J. Chem. Soc., Chem. Commun.* **1996**, 355−356.

(20) Scharf, H.-D.; Plum, H.; Fleischhauer, J.; Schleker, W. *Chem. Ber.* **1979**, *112*, 862−882.

(21) Brown, H. C.; Narla, G. *J. Org. Chem.* **1995**, *60*, 4686−4687.

(22) Identical by comparison of ^1H and ^{13}C NMR data with those reported in ref 18.

(23) Yusufoglu, A.; Anton, S.; Scharf, H.-D. *J. Org. Chem.* **1986**, *51*, 3485−3487.