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Asymmetric Total Syntheses of (+)-Mycoepoxydiene and Related Natural Product (−)-1893A: Application of One-Pot Ring-Opening/Cross/Ring-Closing Metathesis to Construct Their 9-Oxabicyclo[4.2.1]nona-2,4-diene Skeleton

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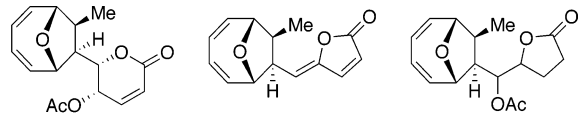
The total syntheses of (+)-mycoepoxydiene and (−)-1893A have been completed. The present synthetic strategy features the use of one-pot ring-opening/cross metathesis (ROM/CM) followed by a ring-closing metathesis (RCM) reaction, allowing for the concise construction of the 9-oxabicyclo-[4.2.1]nona-2,4-diene framework from a 7-oxabicyclo[2.2.1]hept-2-ene derivative and 1,3-butadiene. The sequential metathesis product was converted into (+)-mycoepoxydiene through the oxidative rearrangement of a furfuryl alcohol to a pyranone, thereby establishing its absolute stereochemistry. From the common intermediate, a structurally related natural product (−)-1893A was also synthesized via the vinylogous aldol reaction.

Introduction

(+)-Mycoepoxydiene (**1**) was isolated from the solid-state fermentation of a rare fungus designated as OS-F66617 in 1999 (Figure 1).[1] The structure of **1** was elucidated by extensive spectroscopic studies and finally determined by X-ray crystallographic analysis, although its absolute stereochemistry remained unclear. There had been no publication regarding its biological properties. This fungal metabolite is the first natural product reported so far that contains a 9-oxabicyclo[4.2.1]nona-2,4-diene skeleton.[2] This unprecedented structure is thought to be of polyketide origin.[1] On the other hand, 1893A (**2**) and 1893B (**3**) were isolated recently from the fermentation broth of a marine endophytic fungus (No. 1893), showing cytotoxic and insecticidal activities.[3] The two new metabolic products, **2** and **3**, were found to possess the same oxygen-bridged cyclooctadiene core skeleton. Being interested in their unique structures and the biological activities of **2** and **3**, we became involved in synthetic studies of mycoepoxydiene (**1**) as well as 1893A (**2**) and 1893B (**3**).[4] In a program directed toward the concise synthesis of the core skeleton of these related natural products, we have developed an attractive methodology for the construction of the 9-oxabicyclo[4.2.1]-nona-2,4-diene structure[5] using one-pot ring-opening/cross metathesis (ROM/CM) followed by a ring-closing metathesis (RCM) reaction. Herein, we describe the full details of the asymmetric total syntheses of (+)-**1** and (−)-**2** by the ROM/CM/RCM approach.



(+)-mycoepoxydiene (**1**) (−)-1893A (**2**) 1893B (**3**)

FIGURE 1. Structures of (+)-mycoepoxydiene, (−)-1893A, and 1893B.

Olefin metathesis is established as a remarkably valuable synthetic tool in current organic chemistry.[6] Recently, several new methods using sequential metathesis for the formation of medium- and large-sized ring cycloalkadienes have appeared in the literature. For example, Grubbs and co-workers have explored a ring-expansion reaction via a series of three types of olefin metathesis (ring-opening, cross, and ring-closing metathesis) to yield a variety of 18- to 39-membered macrocycles.[7] Mori and co-workers demonstrated that the ring-

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(1) Cai, P.; McPhail, A. T.; Krainer, E.; Katz, B.; Pearce, C.; Boros, C.; Caceres, B.; Smith, D.; Houck, D. R. *Tetrahedron Lett.* **1999**, *40*, 1479−1482.

(2) Oxygen-bridged dibenzocyclooctadiene lignans such as kadsulignans are known. See: Liu, J.-S.; Li, L. *Phytochemistry* **1995**, *38*, 241−245.

(3) Chen, G.; Lin, Y.; Wen, L.; Vrijmoed, L. L. P.; Jones, E. B. G. *Tetrahedron* **2003**, *59*, 4907−4909. The whole stereochemistry of 1893B (**3**) has not been determined.

(4) The first total synthesis of (±)-**1** was published by us in a preliminary communication. See: Takao, K.; Watanabe, G.; Yasui, H.; Tadano, K. *Org. Lett.* **2002**, *4*, 2941−2943.

(5) Recently, an elegant route to enantiopure 9-oxabicyclo[4.2.1]non-3-ene was reported. See: Paquette, L. A.; Kim, I. H.; Cunière, N. *Org. Lett.* **2003**, *5*, 221−223.

(6) For recent reviews on olefin metathesis, see: (a) Schrock, R. R.; Hoveyda, A. H. *Angew. Chem., Int. Ed.* **2003**, *42*, 4592−4633. (b) Blechert, S.; Connon, S. J. *Angew. Chem., Int. Ed.* **2003**, *42*, 1900−1923. (c) Arjona, O.; Csákÿ, A. G.; Plumet, J. *Eur. J. Org. Chem.* **2003**, 611−622. (d) Trnka, T. M.; Grubbs, R. H. *Acc. Chem. Res.* **2001**, *34*, 18−29. (e) Fürstner, A. *Angew. Chem., Int. Ed.* **2000**, *39*, 3012−3043.

(7) Lee, C. W.; Choi, T.-L.; Grubbs, R. H. *J. Am. Chem. Soc.* **2002**, *124*, 3224−3225.

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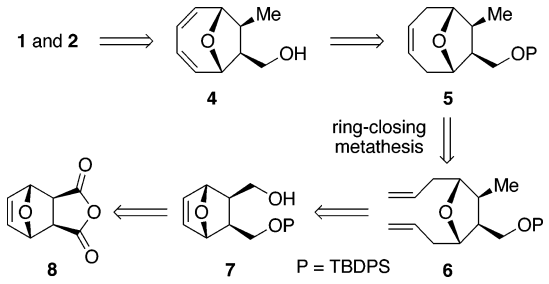
SCHEME 1



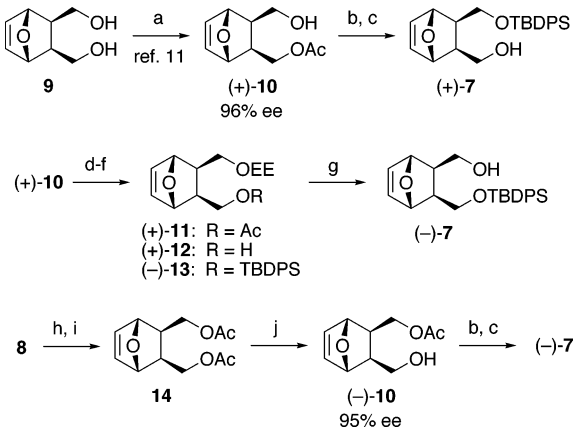
opening and successive ring-closing metathesis of cycloalkene bearing an alkyne side chain proceeded to provide bicyclic compounds and/or dimeric compounds.[8] Kulkarni and Diver reported cycloheptadiene synthesis by tandem intermolecular enyne metathesis between 1-alkynes and cyclopentene.[9] In the present report, we describe the synthesis of the core skeleton of **1** and **2** through two synthetic routes by the use of an intramolecular or sequential inter- and then intramolecular olefin metathesis strategy. The first route relies on the RCM of a doubly 2-propen-1-yl-substituted tetrahydrofuran derivative at C2 and C5. The resulting RCM product, a 9-oxabicyclo[4.2.1]non-3-ene, was transformed into a 9-oxabicyclo[4.2.1]nona-2,4-diene skeleton. Our second route involves one-pot ROM/CM followed by RCM to construct directly the 9-oxabicyclo[4.2.1]nona-2,4-diene skeleton from a functionalized 7-oxabicyclo[2.2.1]hept-2-ene derivative.

Results and Discussion

The First-Generation Approach to the Functionalized Oxygen-Bridged Cyclooctadiene (+)-4. Our first-generation retrosynthetic analysis of **1** and **2** is shown in Scheme 1. We envisioned synthesizing the target compounds **1** and **2** from a common synthetic intermediate, 7,8-dialkylated 9-oxabicyclo[4.2.1]nona-2,4-diene **4**. As a precursor for the oxygen-bridged cyclooctadiene **4**, the oxygen-bridged cyclooctene derivative **5** seemed to be a promising intermediate. The formation of **5** would be achieved by the RCM of 2,5-dipropenylated tetrahydrofuran **6**. The substrate for this RCM reaction was expected to be prepared from a 7-oxabicyclo[2.2.1]-hept-2-ene derivative such as **7**, which in turn could be prepared in an optically active form through asymmetric desymmetrization of a corresponding meso-compound such as the known **8**,[10] the Diels–Alder exo-adduct of furan and maleic anhydride. The chirality incorporated into the ring junction of **8** was anticipated to be preserved throughout the remaining process.

The syntheses of **1** and **2** began with the asymmetric desymmetrization of meso-compounds **9** and **14** by the well-known enzymatic methods (Scheme 2). According to Bloch's precedent,[11] the lipase-catalyzed transesterification of vinyl acetate with *meso*-diol **9**, the hydride-reduction product of **8**,[12] was conducted to afford mono-

SCHEME 2[a]



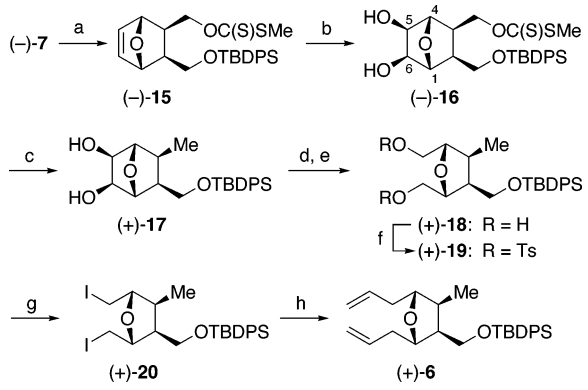
[a] Reagents and conditions: (a) lipase PS (Amano), vinyl acetate, 83%; (b) TBDPSCl, imidazole, DMF; (c) NaOMe, MeOH, 92% for 2 steps; (d) CH_2=CHOEt, PPTS, CH_2Cl_2, 97%; (e) NaOMe, MeOH, quant.; (f) TBDPSCl, imidazole, DMF, quant.; (g) 60% aq AcOH, THF, 97%; (h) $LiAlH_4$, THF; (i) Ac_2O, pyridine, 67% for 2 steps; (j) lipase PS (Amano), THF–H_2O, 88%.

acetate (+)-**10** in an enantiomeric excess (ee) of 96%.[13] Silylation of (+)-**10** followed by deacetylation provided *tert*-butyldiphenylsilyl (TBDPS) ether (+)-**7**. In addition, the enantiomer (−)-**7** was prepared from (+)-**10** via a protection–deprotection sequence, i.e., (1) ethoxyethyl (EE) etherification of the hydroxy group in (+)-**10**, (2) deacetylation, (3) silylation with TBDPSCl, and then (4) deprotection of the EE group under mild acidic conditions. An alternative and more concise synthesis of (−)-**7** was performed from *meso*-diacetate **14**, readily prepared from **8**. By treatment of **14** with lipase PS in THF–H_2O, the enantioselective hydrolysis of one acetyl ester occurred effectively to provide monoacetate (−)-**10** in 95% ee,[13] the antipode of the monoacetate prepared from **9**. By using the same procedure for the preparation of (+)-**7** from (+)-**10**, (−)-**10** was converted into silyl ether (−)-**7**.

As shown in Scheme 3, the functionalized 7-oxabicyclo-[2.2.1]hept-2-ene derivative (−)-**7** was converted into the 2,5-dipropenylated tetrahydrofuran (+)-**6**. For the radical-mediated removal of the hydroxy group, (−)-**7** was converted into the xanthate ester (−)-**15**. Dihydroxylation of the double bond in (−)-**15** with osmium tetroxide and trimethylamine *N*-oxide (TMNO)[14] stereoselectively provided diol (−)-**16**,[15] which was treated with tri-*n*-butyltin hydride to provide the deoxygenated product (+)-**17**.[16] Oxidative cleavage of the cis-diol in (+)-**17** with lead tetraacetate resulted in the formation of a dialdehyde hydrate, the ^{1}H NMR spectrum of which showed no signals attributable to two aldehyde groups. The oxidative cleavage product was reduced with sodium boro-

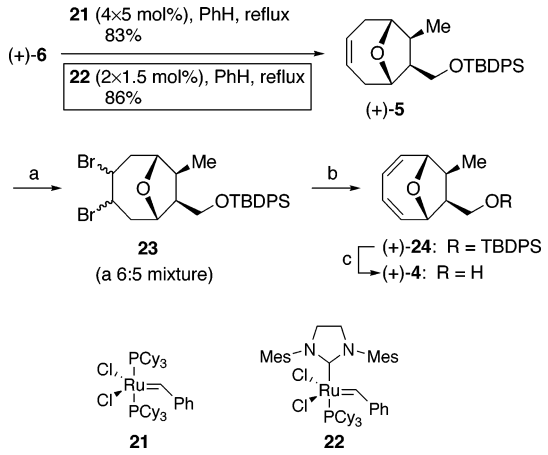
(8) Mori, M.; Kuzuba, Y.; Kitamura, T.; Sato, Y. *Org. Lett.* **2002**, *4*, 3855–3858.
(9) Kulkarni, A. A.; Diver, S. T. *Org. Lett.* **2003**, *5*, 3463–3466.
(10) (a) Woodward, R. B.; Baer, H. *J. Am. Chem. Soc.* **1948**, *70*, 1161–1166. (b) *Chem. Abstr.* **1966**, *65*, 16924e–16925b.
(11) Cinquin, C.; Schaper, I.; Mandville, G.; Bloch, R. *Synlett* **1995**, 339–340.
(12) Das, J.; Vu, T.; Harris, D. N.; Ogletree, M. L. *J. Med. Chem.* **1988**, *31*, 930–935.
(13) The ee values of (+)- and (−)-**10** were determined by chiral HPLC analysis after conversion into the corresponding *p-tert*-butylbenzoates. The absolute stereochemistry of (+)-**10** has been unambiguously determined by Bloch's group.[11]
(14) Ray, R.; Matteson, D. S. *Tetrahedron Lett.* **1980**, *21*, 449–450.
(15) In the ^{1}H NMR spectrum of (−)-**16**, two characteristic coupling constants ($J_{1,6}$ = 0 Hz and $J_{4,5}$ = 0 Hz) were observed. The fact indicated that the dihydroxylation occurred on the β-face of (−)-**15** to provide *exo*-diol (−)-**16**.
(16) An attempt at radical-induced deoxygenation of (−)-**15** with n-Bu_3SnH in the presence of AIBN gave a complex mixture.

SCHEME 3[a]



[a] Reagents and conditions: (a) NaH, CS_2, MeI, THF, 96%; (b) OsO_4, TMNO, aq acetone, 85%; (c) *n*-Bu_3SnH, AIBN, toluene, reflux, 89%; (d) $Pb(OAc)_4$, PhH; (e) $NaBH_4$, MeOH, 81% for 2 steps; (f) *n*-BuLi, TsCl, THF, 0 °C, 79%; (g) NaI, 2-butanone, reflux, 96%; (h) vinylMgBr, PhH, 89%.

SCHEME 4[a]

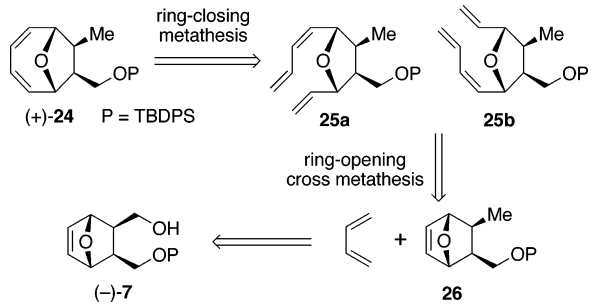


[a] Reagents and conditions: (a) Br_2, Et_2O, −78 °C, 96%; (b) *t*-BuOK, *t*-BuOH, 75 °C, 53%; (c) *n*-Bu_4NF, THF, quant.

hydride to provide tetrahydrofuran 2,5-dimethanol (+)-**18**. With use of *n*-butyllithium as a base, simultaneous ditosylation of (+)-**18** was performed to provide (+)-**19**,[17] which was transformed into diiodide (+)-**20** with sodium iodide in boiling 2-butanone. An attempt to substitute simultaneously the two iodo groups in (+)-**20** with a vinyl group with use of a variety of vinylcopper reagents gave no desired product. Eventually, (+)-**20** was found to react smoothly with an excess amount of vinylmagnesium bromide in the absence of a copper(I) catalyst in benzene at room temperature, providing the 2,5-diallylated tetrahydrofuran (+)-**6**.[18]

With the diene (+)-**6** in hand, the RCM reaction was investigated (Scheme 4). In a high-dilution (0.003 M) solution in refluxing benzene, the substrate (+)-**6** was treated with the first-generation Grubbs catalyst **21**[19]

SCHEME 5



(four-time addition of each 5 mol % equiv of **21** over a period of 20 h) to provide the oxygen-bridged cyclooctene (+)-**5** in 83% yield.[20] Increasing the concentration of (+)-**6** in benzene (0.005 M) decreased the yield to 70%, presumably due to the co-occurrence of competing oligomerization. The use of the second-generation Grubbs catalyst **22**[21] enabled the reduction of the total amount of catalyst to 3 mol % and the reduction of the reaction time to 6 h, with the formation of (+)-**5** in a slightly higher yield of 86%. Then we explored the introduction of the diene unit in the 9-oxabicyclo[4.2.1]nonene ring. The addition of 1 equiv of bromine to (+)-**5** and the subsequent *β*-elimination of two-molar hydrogen bromide from the resulting stereoisomeric mixture of dibromide **23**, with potassium *tert*-butoxide in hot *tert*-butyl alcohol, provided the desired 9-oxabicyclo[4.2.1]nona-2,4-diene (+)-**24**. The fluoride-mediated desilylation of (+)-**24** provided the advanced synthetic intermediate (+)-**4**. The first-generation synthesis of the enantiomerically enriched oxygen-bridged cyclooctadiene (+)-**4** required 17 steps in 13.6% overall yield from *meso*-diol **9** or 15 steps in 14.1% overall yield from *meso*-diacetate **14**.

The Second-Generation Access to (+)-4 by Using the ROM/CM/RCM Approach. To streamline the synthetic route to the 9-oxabicyclo[4.2.1]nona-2,4-diene structure, we undertook the development of a methodology based on sequential metathesis. Our second-generation synthetic approach is summarized in Scheme 5. In this novel approach, the construction of oxygen-bridged cyclooctadiene (+)-**24** was expected to be performed by the RCM of triene **25a** or **25b**, which in turn would be synthesized by the ring-opening/cross metathesis (ROM/CM) of 7-oxabicyclo[2.2.1]hept-2-ene **26** with 1,3-butadiene. The intermediate **26** would be prepared from (−)-**7**. This sequential ROM/CM/RCM approach seemed particularly attractive because the 9-oxabicyclo[4.2.1]-nona-2,4-diene skeleton can be formed from 7-oxabicyclo-[2.2.1]hept-2-ene in fewer steps.

Although 7-oxabicyclo[2.2.1]hept-2-ene derivatives are known to undergo ring-opening metathesis generating a variety of functionalized compounds,[22] precedents for successive cross metathesis with use of 1,3-butadiene are

(17) Use of pyridine in place of the *n*-BuLi/THF system resulted in the undesired intramolecular cyclization of intermediary monotosylate, providing a 3,8-dioxabicyclo[3.2.1]octane derivative.

(18) When tetrahydrofuran was used as the solvent, the reaction proceeded less effectively.

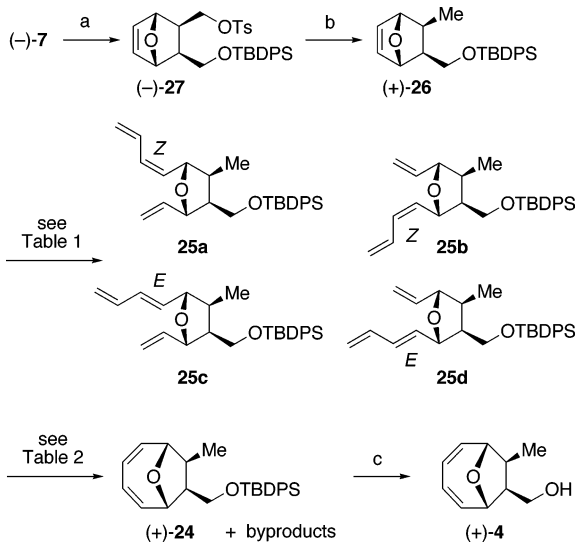
(19) (a) Schwab, P.; France, M. B.; Ziller, J. W.; Grubbs, R. H. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 2039−2041. (b) Schwab, P.; Grubbs, R. H.; Ziller, J. W. *J. Am. Chem. Soc.* **1996**, *118*, 100−110.

(20) When 20 mol % of **21** was added in one portion, the product (+)-**5** was obtained in 41% yield.

(21) Scholl, M.; Ding, S.; Lee, C. W.; Grubbs, R. H. *Org. Lett.* **1999**, *1*, 953−956.

(22) (a) Schneider, M. F.; Lucas, N.; Velder, J.; Blechert, S. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 257−259. (b) Arjona, O.; Csáky, A. G.; Murcia, M. C.; Plumet, J. *J. Org. Chem.* **1999**, *64*, 9739−9741. Also see refs 6b and 6c.

SCHEME 6[a]



[a] Reagents and conditions: (a) TsCl, Et_3N, DMAP, CH_2Cl_2, quant.; (b) $NaBH_4$, DMPU, 90 °C, 76%; (c) *n*-Bu_4NF, THF.

TABLE 1. The Ring-Opening/Cross Metathesis of (+)-26 with 1,3-Butadiene

entry	conditions[a]	yield,[b] %	*Z*/*E*[c]
1	**21**, benzene (0.01 M), rt	60	1.8:1
2	**22**, benzene (0.01 M), rt	40	1:1.2
3	**21**, CH_2Cl_2 (0.01 M), rt	59	1.5:1
4	**22**, CH_2Cl_2 (0.01 M), rt	50	1:2.3
5[d]	**21**, benzene (0.01 M), rt	75	1.5:1

[a] Unless otherwise noted, 2 equiv of 1,3-butadiene and 5 mol % of catalyst **21** or **22** were used. [b] Combined yield for **25a**–**d**. [c] Determined by ^1H NMR (270 MHz). [d] 4 equiv of 1,3-butadiene was used.

scarce.[23] To confirm the feasibility of the designed approach, we first examined the two reactions in a stepwise manner. The substrate (+)-**26** was prepared from (−)-**7** through tosylation followed by the reductive removal of the sulfonate in the resultant (−)-**27** with sodium borohydride in *N,N′*-dimethylpropyleneurea (DMPU) (Scheme 6). The results for the first ROM/CM of (+)-**26** with 1,3-butadiene are summarized in Table 1. With use of the first-generation Grubbs catalyst **21** in benzene (entry 1), the reaction proceeded smoothly at room temperature to give a mixture of trienes with a favorable formation of a mixture of the *Z*-isomers **25a** and **25b**, which were indispensable for the next ring-closing step.[24] In contrast, the second-generation Grubbs catalyst **22** produced preferentially the undesired *E*-isomers (**25c** and **25d**) in a diminished yield of 40% (entry 2). Lower *Z*-selectivity was also observed when the reaction was conducted in dichloromethane (entries 3 and 4). To prevent a competing self-metathesis (polymerization) of the 7-oxabicyclo[2.2.1]-hept-2-ene, an excess (4 equiv) of 1,3-butadiene was employed (entry 5). As expected, the yield was improved with a minimal decrease in the *Z*/*E*-selectivity. As shown in Table 2, the RCM reaction of the mixture of trienes **25a**–**d** occurred more effectively by use of the catalyst **22** in refluxing benzene (entry 2), affording the 9-oxabicyclo[4.2.1]nona-2,4-diene compound (+)-**24** accompanied by inseparable and unidentified byproducts. By exposure of the mixture to tetrabutylammonium fluoride, homogeneous (+)-**4** was obtained in a yield of 29% after chromatography on silica gel. The first-generation catalyst **21** did not catalyze the cyclization (entry 1). Whereas the RCM of (+)-**6** smoothly produced the 9-oxabicyclo-[4.2.1]non-3-ene (+)-**5** as shown in Scheme 4, that of **25a**–**d** proceeded much more slowly and less effectively. The solvent did not affect this reaction (entries 2–4).[25] Assuming that a lone pair of electrons of the bridge-oxygen might diminish the catalyst reactivity, we also attempted RCM in the presence of titanium tetraisopropoxide[26] (entry 5). Under these conditions, the desired product (+)-**4** was obtained in a lower yield of 10% after desilylation.

TABLE 2. The Ring-Closing Metathesis of 25a–d

entry	conditions[a]	yield of **4**,[b] %
1	**21**, benzene (0.003 M), reflux	2
2	**22**, benzene (0.003 M), reflux	29
3	**22**, CH_2Cl_2 (0.003 M), reflux	28
4	**22**, toluene (0.003 M), reflux	27
5[c]	**22**, Ti(O-*i*-Pr)$_4$, benzene (0.003 M), reflux	10

[a] Triene substrates **25a**–**d** were prepared by using the procedure of entry 1 in Table 1. 20 mol % of catalyst **21** or **22** was used. [b] Isolated yield of (+)-**4** after desilylation. [c] 1 equiv of Ti(O-*i*-Pr)$_4$ was used.

To construct the 9-oxabicyclo[4.2.1]nona-2,4-diene structure from the 7-oxabicyclo[2.2.1]hept-2-ene derivative more concisely,[27] we next performed the sequential ROM/CM/RCM reaction in a one-pot process using the substrates (+)-**26**, (+)-**28**, and (−)-**13** (Scheme 7). The treatment of (+)-**26** with 1,3-butadiene (2 equiv) in the presence of **21** (2 mol %) in benzene (0.006 M) at room temperature initially produced trienes **25a**–**d**. After (+)-**26** was consumed, the reaction mixture was heated to reflux and bubbled in a stream of argon to remove excess 1,3-butadiene. Then each 2 mol % of **22** was added in five portions over a period of 4 days. Desilylation of the reaction mixture provided the key intermediate (+)-**4** in a yield of 23% from (+)-**26**. When 4 equiv of 1,3-butadiene was used in this one-pot reaction, the yield was decreased, contrary to our expectation. The ROM/CM/RCM reaction of substrate (+)-**28**, prepared from (+)-**26** by desilylation, proceeded less effectively. On the other hand, the di-*O*-protected diol derivative (−)-**13** underwent one-pot ROM/CM/RCM to afford (+)-**30**, after removal of the ethoxyethyl group, in almost the same yield as that

(23) (a) Randall, M. L.; Tallarico, J. A.; Snapper, M. L. *J. Am. Chem. Soc.* **1995**, *117*, 9610–9611. (b) Michaut, M.; Parrain, J.-L.; Santelli, M. *Chem. Commun.* **1998**, 2567–2568.

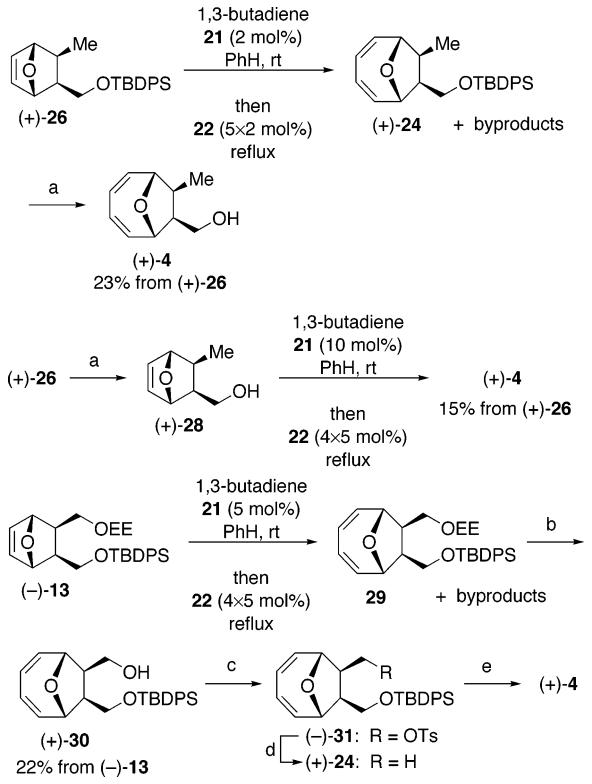
(24) The Grubbs group reported that treatment of **21** with a 10-fold excess of 1,3-butadiene resulted in the high-yield formation of a vinylalkylidene carbene $RuCl_2(=CHCH=CH_2)(PCy_3)_2$ and that no formation of a methylidene carbene $RuCl_2(=CH_2)(PCy_3)_2$ occurred even after a prolonged reaction time.[19b] We presume that the vinylalkylidene ruthenium complex, which behaves as an active catalytic species, is initially formed. For the reaction mechanism of ROM/CM, see ref 23.

(25) For discussions regarding the effect of solvent and reaction temperatures in metathesis, see: (a) Fürstner, A.; Thiel, O. R.; Ackermann, L.; Schanz, H.-J.; Nolan, S. P. *J. Org. Chem.* **2000**, *65*, 2204–2207. (b) Yamamoto, K.; Biswas, K.; Gaul, C.; Danishefsky, S. J. *Tetrahedron Lett.* **2003**, *44*, 3297–3299.

(26) Fürstner, A.; Langemann, K. *J. Am. Chem. Soc.* **1997**, *119*, 9130–9136.

(27) Under the ROM/CM conditions described in Table 1, no formation of the 9-oxabicyclo[4.2.1]nona-2,4-diene skeleton was observed.

SCHEME 7[a]

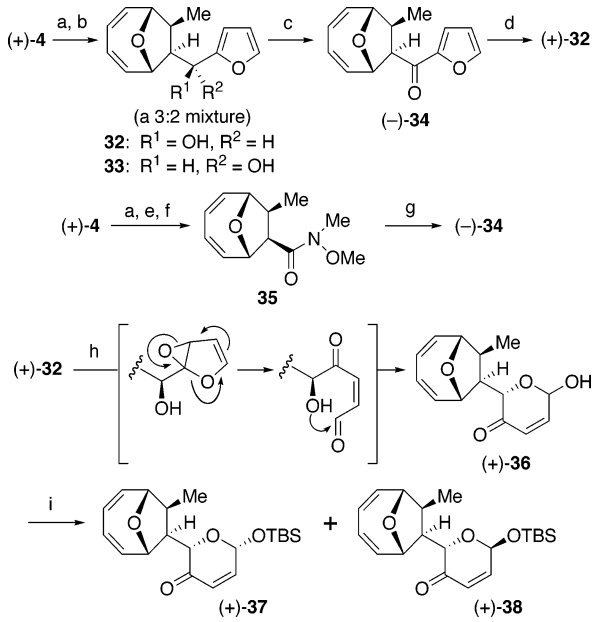


[a] Reagents and conditions: (a) *n*-Bu_4NF, THF; (b) PPTS, MeOH; (c) TsCl, Et_3N, DMAP, CH_2Cl_2, quant.; (d) $NaBH_4$, DMPU, 90 °C, 76%; (e) *n*-Bu_4NF, THF, quant.

obtained in the case of (+)-**26**.[28] The product (+)-**30** was deoxygenated to (+)-**4** via tosylate (−)-**31**. Although the yield is still moderate, the present one-pot ROM/CM/RCM approach realizes access to (+)-**4** in 10 steps with an overall yield of 13.7% from *meso*-diol **9** or in 8 steps from *meso*-diacetate **14** with a 14.2% overall yield.

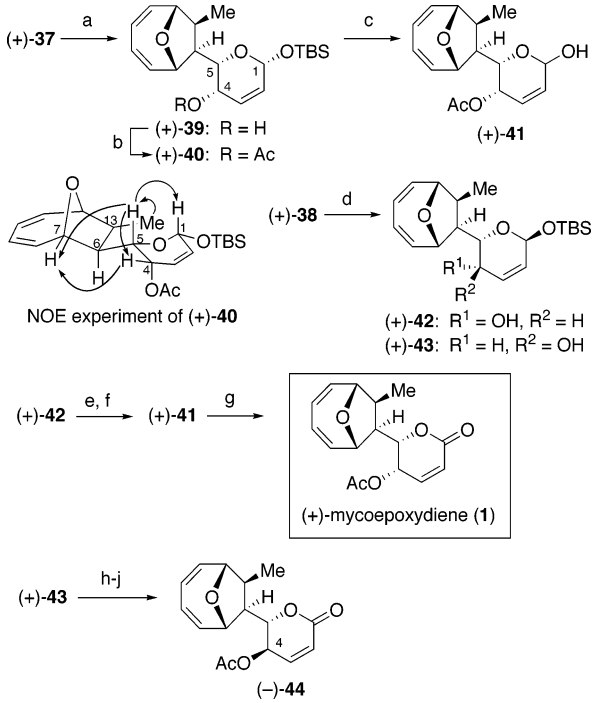
Completion of the Synthesis of (+)-Mycoepoxydiene (1). Having established a practical synthetic route to the 9-oxabicyclo[4.2.1]nona-2,4-diene intermediates, we next focused our efforts on the assembly of the δ-lactone moiety attached to the main scaffold. The key step in achieving this purpose was the oxidative rearrangement of a furfuryl alcohol, incorporated into the main scaffold, to a hydroxylated pyranone.[29] The total synthesis of (+)-**1** is illustrated in Schemes 8 and 9. Oxidation of (+)-**4** with a Dess−Martin reagent[30] provided the corresponding aldehyde, which was reacted with 2-furyllithium derived from furan and *n*-butyllithium, providing an inseparable diastereomeric mixture (ca. 3:2) of **32** and **33**. For the synthesis of **1**, the diastereomer **32** possesses the correct stereochemistry. Thus, more efficient preparation of **32** was explored and accomplished by an oxidation−reduction procedure. The mixture of furfuryl alcohols **32** and **33** was oxidized to

SCHEME 8[a]



[a] Reagents and conditions: (a) Dess−Martin periodinane, CH_2Cl_2; (b) furan, *n*-BuLi, THF, 0 °C, 43% for 2 steps; (c) MnO_2, CH_2Cl_2, 72%; (d) L-Selectride, THF, −78 °C, 85%; (e) $NaClO_2$, NH_2SO_3H, Na_2HPO_4, *t*-BuOH−H_2O; (f) Me(MeO)NH·HCl, EDC·HCl, HOBt, Et_3N, DMAP, CH_2Cl_2; (g) furan, *n*-BuLi, THF, 0 °C, 43% from (+)-**4**; (h) VO(acac)$_2$, *t*-BuOOH, CH_2Cl_2, 0 °C, 90%; (i) TBSCl, Et_3N, DMAP, CH_2Cl_2, 46% for (+)-**37** and 19% for (+)-**38**.

SCHEME 9[a]



[a] Reagents and conditions: (a) $NaBH_4$, $CeCl_3·7H_2O$, MeOH−CH_2Cl_2, −78 °C, 86%; (b) Ac_2O, DMAP, pyridine, 89%; (c) aq HCl, THF, quant.; (d) $NaBH_4$, $CeCl_3·7H_2O$, MeOH, 0 °C, 63% for (+)-**42** and 30% for (+)-**43**; (e) Ac_2O, DMAP, pyridine; (f) aq HCl, THF, 80% for 2 steps; (g) MnO_2, CH_2Cl_2, 76%; (h) Ac_2O, DMAP, pyridine; (i) aq HCl, THF; (j) MnO_2, CH_2Cl_2, 65% for 3 steps.

(−)-**34** with manganese dioxide. Reduction of the carbonyl group in (−)-**34** with L-Selectride provided the desired

(28) It was confirmed that the ROM/CM of (−)-**13** with use of **21** in benzene produced preferentially the *Z*-isomers (*Z*/*E* = 1.6:1).

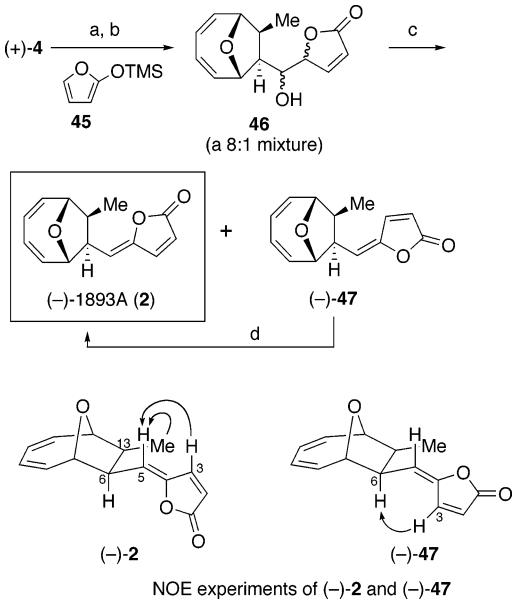
(29) For a review on furan as a building block in organic synthesis, see: Maier, M. In *Organic Synthesis Highlights II*; Waldmann, H., Ed.; VCH: Weinheim, Germany, 1995; pp 231−242.

(30) (a) Dess, D. B.; Martin, J. C. *J. Org. Chem.* **1983**, *48*, 4155−4156. (b) Dess, D. B.; Martin, J. C. *J. Am. Chem. Soc.* **1991**, *113*, 7277−7287. (c) Ireland, R. E.; Liu, L. *J. Org. Chem.* **1993**, *58*, 2899.

furfuryl alcohol (+)-**32** as a sole product. This reduction proceeded possibly through the Li-chelation-assisted transition state occurring between the carbonyl group and the bridge oxygen. A more efficient route to ketone (−)-**34** was achieved as follows. The primary alcohol in (+)-**4** was oxidized to the carboxylic acid by two-step oxidation, which was coupled with *N,O*-dimethylhydroxylamine by using water-soluble carbodiimide to provide the Weinreb amide **35**. The addition of 2-furyllithium to **35** afforded the ketone (−)-**34** in an improved yield of 43% from (+)-**4**. Among the known methods for the rearrangement of furfuryl alcohols to pyranones,[29] the procedure with vanadium-mediated oxidation conditions[31] seemed to be well-suited to (+)-**32** because these conditions were expected to prevent the oxidation of the diene in the eight-membered ring. In fact, the treatment of (+)-**32** with *tert*-butyl hydroperoxide in the presence of a catalytic amount of vanadyl acetylacetonate ($VO(acac)_2$) effectively provided the rearranged product (+)-**36** as a 2:1 hemiacetal mixture through the rearrangement depicted in brackets.[32] Protection of the hemiacetal hydroxy group in (+)-**36** as the *tert*-butyldimethylsilyl (TBS) ether gave a 2.4:1 mixture of α-isomer (+)-**37** and β-isomer (+)-**38**, which were readily separated.

The stereoselective 1,2-reduction of the major product (+)-**37** was conducted under Luche conditions[33] to afford allylic alcohol (+)-**39** exclusively, which was converted into acetate (+)-**40** (Scheme 9). The stereochemistry of (+)-**40** was confirmed by ^{1}H NMR analysis, including NOE experiments.[34] Consequently, the configurations of stereogenic centers introduced by the L-Selectride reduction of (−)-**34** (C5, mycoepoxydiene numbering) and by the Luche reduction of (+)-**37** (C4) were determined as depicted. By hydrolysis with dilute hydrochloric acid, the TBS group in (+)-**40** was removed to provide lactol (+)-**41**. The minor diastereomer (+)-**38** was also converted into (+)-**41** by using the same procedure as that described for the transformation of (+)-**37** to (+)-**41**. The less stereoselective result was observed in the Luche reduction of (+)-**38**. The stereoselectivity of the reduction of (+)-**38** was affected by the reaction temperature. When the reaction was carried out at −78 °C, the ratio of (+)-**42** to (+)-**43** was 1:2. At 0 °C, the desired (+)-**42** was obtained favorably (dr = 2:1). Finally, the lactol (+)-**41** was oxidized to (+)-mycoepoxydiene (**1**) with manganese dioxide. The spectroscopic data (^{1}H and ^{13}C NMR) of synthetic (+)-**1** were well matched with those reported for natural **1**.[1,35] Comparison of the specific rotation of synthetic (+)-**1** ($[\alpha]^{20}_D$ +227; *c* 0.072, MeOH) with that of the natural product ($[\alpha]_D$ +210; *c* 0.106, MeOH) established the absolute stereochemistry as depicted in Scheme 9. Analogously, the unnatural enantiomer (−)-mycoepoxydiene (**1**) ($[\alpha]^{19}_D$ −223; *c* 0.093, MeOH) was synthesized from (+)-**7** by using exactly the same synthetic steps as those used for the total synthesis of (+)-**1**. Furthermore, the minor reduction product (+)-**43** was converted into the 4-epimer of (+)-mycoepoxydiene (−)-**44**, which apparently showed different spectra (^{1}H and ^{13}C NMR) from those of **1**.

SCHEME 10[a]



[a] Reagents and conditions: (a) Dess−Martin periodinane, CH_2Cl_2; (b) **45**, TESOTf, CH_2Cl_2, −78 °C, 60% for 2 steps; (c) MsCl, pyridine, rt to 80 °C for 2 days, 63% for (−)-**2** and 13% for (−)-**47**; (d) MsCl, pyridine, 90 °C, 63% for (−)-**2** and 25% for recovered (−)-**47**.

Total Synthesis of (−)-1893A (2). The total synthesis of (−)-1893A (**2**) was achieved from the advanced intermediate (+)-**4** as shown in Scheme 10. As a butenolide anion equivalent, 2-(trimethylsilyloxy)furan (**45**) was chosen due to its high γ-regioselectivity.[36] Thus, oxidation of (+)-**4** and the subsequent vinylogous aldol reaction of the resulting aldehyde with **45** in the presence of triethylsilyl triflate (TESOTf)[37] provided γ-adduct **46** as a mixture of stereoisomers (ca. 8:1).[38,39] The sulfonylation of **46** with methanesulfonyl chloride (MsCl) in pyridine, followed by heating at 80 °C for 30 min,[40] gave (−)-1893A (**2**) and its *E*-isomer (−)-**47** in 45% and 38% yields, respectively. Gratifyingly, a prolonged reaction time (2 days) for converting **46** into the mixture of (−)-**2** and (−)-**47** increased the *Z*:*E* ratio to ca. 5:1, and a 63% yield of (−)-**2** was isolated. In addition, the minor product (−)-**47** was subjected to the same conditions (MsCl, pyridine) to afford additional (−)-**2**. This result is reasonably attributable to a reversible conjugate addition of a nucleophilic species such as a chloride ion to δ-position

(31) Ho, T.-L.; Sapp, S. G. *Synth. Commun.* **1983**, *13*, 207−211.
(32) Reproducible results were obtained by a nonaqueous workup. For an example of water-unstable hemiacetal, see: Trost, B. M.; King, S. A.; Schmidt, T. *J. Am. Chem. Soc.* **1989**, *111*, 5902−5915.
(33) Gemal, A. L.; Luche, J.-L. *J. Am. Chem. Soc.* **1981**, *103*, 5454−5459.
(34) When H5 was irradiated, significant signal enhancements of H1 (14%), H4 (7.6%), and H7 (6.9%) were observed. The lack of signal enhancement of H6 as well as a large coupling constant ($J_{5,6}$ = 10.8 Hz) indicated that H5 and H6 are in an antiperiplanar relationship. NOEs between H4/H7 (9.6%) and H5/CH_3-13 (9.3%) were also observed.
(35) The optical purity of synthetic (+)-**1** was confirmed by chiral HPLC analysis to be 94%.
(36) For a review regarding vinylogous aldol reactions, see: Casiraghi, G.; Zanardi, F.; Appendino, G.; Rassu, G. *Chem. Rev.* **2000**, *100*, 1929−1972.
(37) Jefford, C. W.; Jaggi, D.; Boukouvalas, J. *Tetrahedron Lett.* **1987**, *28*, 4037−4040.
(38) The configurations of the two introduced stereogenic centers in each diastereomer of **46** could not be determined.
(39) By using the mixture **46**, the total synthesis of 1893B (**3**) was also investigated. But we have not succeeded in the synthesis of **3** from **46** yet. Synthetic studies of **3** are now in progress.
(40) Pohmakotr, M.; Tuchinda, P.; Premkaisorn, P.; Reutrakul, V. *Tetrahedron* **1998**, *54*, 11297−11304.

(C5), followed by β-elimination, leading to (−)-**2**. On the basis of the NOE experiment as shown in Scheme 10, the stereochemistries including geometrical structures of (−)-**2** and (−)-**47** were established.[41] Furthermore, the relative configuration of natural **2** was originally confirmed by X-ray crystallographic analysis.[3] The spectroscopic data (IR, ^{1}H and ^{13}C NMR, HRMS) of synthetic (−)-**2** matched well those for natural **2**:[42] therefore it is sure that naturally occurring 1893A (**2**) and our synthetic (−)-**2** possess the same relative stereochemistry. On the other hand, the discrepancy in the absolute value of specific rotation between synthetic and natural **2** was observed. While our synthetic sample had $[\alpha]^{23}_D$ −285 (*c* 0.064, acetone) or $[\alpha]^{22}_D$ −293 (*c* 0.32, acetone), the specific rotation of natural **2** was reported to be $[\alpha]^{20}_D$ +4.0 (*c* 0.07, acetone) in the original isolation paper.[3] Later, the authors revised the value of $[\alpha]_D$ to +148.[43] As the amount of the existing natural sample was so small, we could not examine a direct comparison.

Biological Activities of Mycoepoxydiene. The establishment of the total synthesis of mycoepoxydiene (**1**) provided an opportunity to investigate the unknown biological activity of this natural product. As a result of biological studies with synthetic samples, natural (+)-**1** and unnatural (−)-**1** were both found to show cytotoxicity toward human tumor cells in vitro with IC_{50}s (μg/mL) of 2.3 for (+)-**1** and 1.8 for (−)-**1** against human chronic myelogenous leukemia, K562, and of 3.1 for (+)-**1** and 2.2 for (−)-**1** against human hepatocellular carcinoma, HepG2. Compounds (+)-**1** and (−)-**1** did not show any antibacterial activities against a variety of Gram-positive and Gram-negative bacteria.

(41) In the case of (−)-**2**, a signal enhancement of H5 (4.5%) was observed when H3 was irradiated, whereas NOE was observed between H3 and H6 (11.1%) in (−)-**47**. When CH_3-13 in (−)-**2** was irradiated, a signal enhancement at H5 (4.5%) was also observed. It was confirmed that no epimerization at C6 occurred under Dess−Martin oxidation and/or the vinylogous aldol reaction conditions.

(42) For the spectroscopic comparison of natural and synthetic **2** (^{1}H and ^{13}C NMR), see the Supporting Information.

(43) Chen, G. Personal communication. They explained that their miscalculation caused this change.

Conclusion

We have accomplished the asymmetric total syntheses of (+)-mycoepoxydiene (**1**) and (−)-1893A (**2**). For the construction of the core skeleton, a new methodology based on an ROM/CM/RCM approach has been developed. Thus, ROM/CM of 7-oxabicyclo[2.2.1]hept-2-ene (+)-**26** with 1,3-butadiene, followed by RCM of the resulting trienes **25a**−**d**, produced 9-oxabicyclo[4.2.1]-nona-2,4-diene (+)-**4**. For the conversion of (+)-**4** into the desired natural product (+)-mycoepoxydiene (**1**), we applied the rearrangement of a furfuryl alcohol appendage to a pyranone form. Through the present completion of the total synthesis of (+)-**1**, the absolute stereochemistry of natural **1** was established. The total synthesis of novel natural product (−)-1893A (**2**) was also achieved by use of the vinylogous aldol reaction with 2-(trimethylsilyloxy)furan (**45**) as the introduction of the side chain. Through the two total syntheses, we have verified that the ROM/CM/RCM strategy is a valuable approach to synthesize oxygen-bridged cyclooctadiene-type natural products.

Acknowledgment. We thank Professors Yongcheng Lin (Zhongshan University) and Guangying Chen (City University of Hong Kong) for providing spectral copies of natural **2** and information on the optical rotation for **2**. We also thank Infectious Disease Research Labs., Meiji Seika Kaisha, Ltd., for performing the biological assays for **1**, and Amano Enzyme, Inc., for donating lipase PS. Professor Takeshi Sugai (Keio University) provided us helpful advice regarding the enzymatic experiment, to whom our thanks are due.

Supporting Information Available: Experimental procedures, full characterization data, and ^{1}H and ^{13}C NMR spectra for new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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