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Total Synthesis of (±)-Mycoepoxydiene, a Novel Fungal Metabolite Having an Oxygen-Bridged Cyclooctadiene Skeleton

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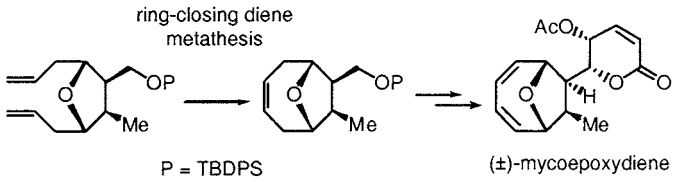
ABSTRACT

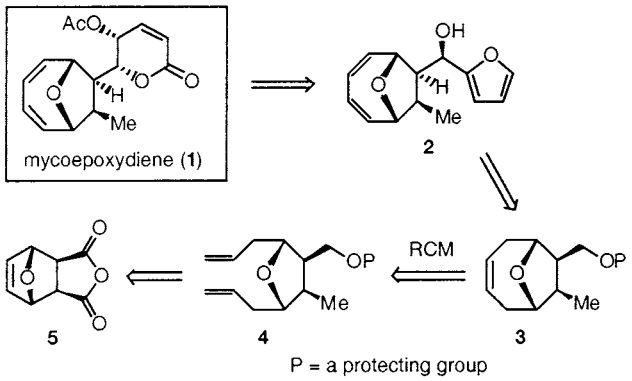


The first total synthesis of (±)-mycoepoxydiene has been accomplished. A ring-closing olefin metathesis (RCM) approach was employed for the construction of the oxygen-bridged eight-membered bicyclic skeleton. The RCM product was converted to the target natural product featuring the oxidative rearrangement of a furfuryl alcohol introduced as the side chain and the stereoselective 1,2-reduction of a *δ*-keto-*β*,*γ*-unsaturated α-lactol intermediate.

Mycoepoxydiene (**1**) (Scheme 1) was isolated from the fermentation of a rare fungus designated as OS-F66617 in 1999.[1] Its gross structure and relative stereochemistry were determined by spectral and X-ray crystallographic analyses, but the absolute stereochemistry is still unknown.[1] This metabolic product was found to possess a structural novelty that consists of an oxygen-bridged cyclooctadiene core skeleton and a functionalized *δ*-lactone. Although oxygen-bridged dibenzocyclooctadiene lignans such as kadsulignans are known,[2] compound **1** is, to the best of our knowledge, the only reported natural product containing a 9-oxabicyclo-[4.2.1]nona-2,4-diene skeleton without a fused biphenyl system. This unique structural feature prompted us to attempt the total synthesis of **1**. Herein we report the first total synthesis of (±)-mycoepoxydiene featuring a ring-closing diene metathesis (RCM) approach to the construction of the core oxygen-bridged eight-membered carbocyclic skeleton.

Recently, RCM has received a great deal of attention in the synthesis of medium- and large-sized rings from acyclic dienes. A large number of applications to natural product synthesis have revealed the versatility of the RCM reaction.[3] We envisaged the use of the RCM strategy as a means to

Scheme 1



(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) Liu, J.-S.; Li, L. *Phytochemistry* **1995**, *38*, 241−245.

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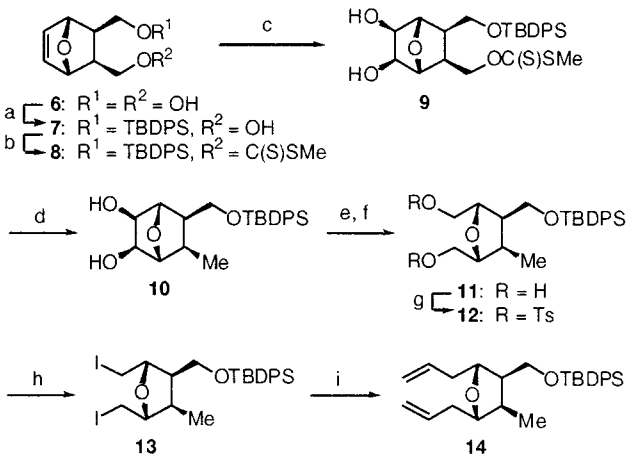
access the core skeleton of **1**.[4] Our retrosynthetic analysis of **1** is shown in Scheme 1. The α,β-unsaturated δ-lactone moiety of **1** would be constructed at a later stage of total synthesis by employing the oxidative rearrangement of a furfuryl alcohol to a hydroxylated pyranone.[5] The requisite furfuryl alcohol derivative **2** could be prepared using the coupling of an aldehyde derivative derived from bicyclic intermediate **3** with furan as a key step. The 9-oxabicyclo-[4.2.1]non-3-ene derivative **3** was expected to be obtained by the RCM reaction of diene **4**, which in turn would be prepared from the known **5**,[6] the Diels−Alder adduct of furan and maleic anhydride.

The synthesis began with the preparation of **14** (P = TBDPS in **4**), the substrate for the RCM reaction (Scheme 2). Monosilylation of *meso*-diol **6**, prepared from **5** by a known procedure,[7] was conducted with sodium hydride and *tert*-butyldiphenylsilyl chloride (TBDPSCl). The resulting mono-*O*-TBDPS derivative **7** was converted to xanthate ester **8** using standard reaction conditions. The treatment of **8** with osmium tetroxide and trimethylamine-*N*-oxide (TMNO)[8] underwent stereoselective dihydroxylation to give *exo*-diol **9**, which was subjected to the tri-*n*-butyltin hydride reduction of the xanthate ester to provide deoxygenated product **10** efficiently. The oxidative cleavage of the vicinal diol in **10** with lead tetraacetate followed by the sodium borohydride reduction of the resulting dialdehyde hydrate provided a tetrasubstituted tetrahydrofuran derivative **11**. The 1,4-carbinols in **11** were converted simultaneously to diiodo derivative **13** via the corresponding ditosylate **12**. Simultaneous substitution of the two iodo groups in **13**, each by a vinyl group, was achieved efficiently using an excess amount of vinylmagnesium bromide in benzene, affording 1,4-diallylated tetrahydrofuran **14**.[9]

With the designed diene **14** in hand, the RCM reaction was next examined (Scheme 3). The treatment of **14** with a Grubbs catalyst **15**[10] (four additions, each of 5 mol % **15** over a period of 20 h) in refluxing benzene furnished the desired oxygen-bridged cyclooctene derivative **16** (P = TBDPS in **3**) in an 83% yield.[11] In this case, a highly diluted solution (0.003 M) of **14** in benzene was essential to obtain a satisfactory result.[12] The addition of bromine to **16**, followed by the exposure of the resulting vicinal dibromo adduct **17** as a diastereomeric mixture to potassium *t*-butoxide, provided a 9-oxabicyclo[4.2.1]nona-2,4-diene derivative **18**.[13]

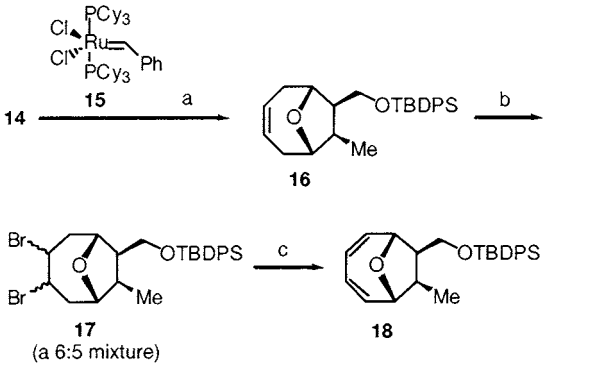
Having established the synthetic route to the oxygen-bridged cyclooctadiene skeleton, we turned our attention to the construction of the δ-lactone moiety attached to the main scaffold (Scheme 4). The desilylation of **18** with tetra-*n*-

Scheme 2[a]



[a] Reagents and conditions: (a) NaH, TBDPSCl, THF, 92%; (b) NaH, CS_2, MeI, THF, 85%; (c) OsO_4, TMNO, aqueous acetone; (d) *n*-Bu_3SnH, AIBN, toluene, reflux, 88% for two steps; (e) $Pb(OAc)_4$, PhH; (f) $NaBH_4$, MeOH, 84% for two steps; (g) *n*-BuLi, TsCl, THF, 0 °C, 89%; (h) NaI, 2-butanone, reflux, 95%; (i) vinylMgBr, PhH, 80%.

Scheme 3[a]



[a] Reagents and conditions: (a) **15** (20 mol %), PhH, reflux, 83%; (b) Br_2, Et_2O, −78 °C, 88%; (c) *t*-BuOK, *t*-BuOH, 75 °C, 58%.

(3) For recent reviews regarding the ring-closing metathesis, see: (a) Yet, L. *Chem. Rev.* **2000**, *100*, 2963−3007. (b) Fürstner, A. *Angew. Chem., Int. Ed.* **2000**, *39*, 3012−3043. (c) Grubbs, R. H.; Chang, S. *Tetrahedron* **1998**, *54*, 4413−4450. (d) Armstrong, S. K. *J. Chem. Soc., Perkin Trans. 1* **1998**, 371−388.

(4) While this work was in progress, a metathesis strategy for preparing a 9-oxabicyclo[4.2.1]non-3-ene system was reported; see: Hanna, I.; Michaut, V. *Org. Lett.* **2000**, *2*, 1141−1143.

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

(6) (a) Woodward, R. B.; Baer, H. *J. Am. Chem. Soc.* **1948**, *70*, 1161−1166. (b) *Chem. Abstr.* **1966**, *65*, 16924e.

(7) Das, J.; Vu, T.; Harris, D. N.; Ogletree, M. L. *J. Med. Chem.* **1988**, *31*, 930−935.

(8) Ray, R.; Matteson, D. S. *Tetrahedron Lett.* **1980**, *21*, 449−450.

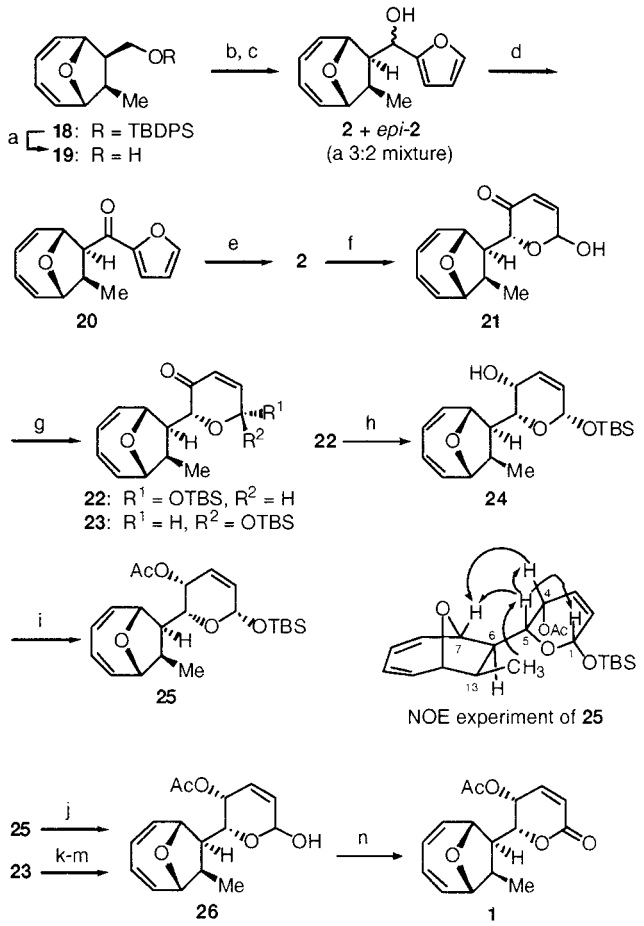
(9) When tetrahydrofuran was used as the solvent, the reaction proceeded less effectively. Neither vinylcopper reagents nor vinyllithium provided superior results.

(10) (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) Byproducts derived from the catalyst were removed effectively by treatment with dimethyl sulfoxide; see: Ahn, Y. M.; Yang, K.; Georg, G. I. *Org. Lett.* **2001**, *3*, 1411−1413.

(12) Increasing the concentration of **14** in benzene resulted in a lowering of the yield of **16**, presumably due to the occurrence of competing oligomerization. On the other hand, the RCM reaction in dichloromethane gave decomposed materials.

Scheme 4[a]



[a] Reagents and conditions: (a) *n*-Bu_4NF, THF, 99%; (b) Dess−Martin periodinane, CH_2Cl_2; (c) furan, *n*-BuLi, THF, 0 °C, 67% for two steps; (d) MnO_2, CH_2Cl_2, 78%; (e) L-Selectride, THF, −78 °C, 95%; (f) $VO(acac)_2$, *t*-BuOOH, CH_2Cl_2, 0 °C, 76%; (g) TBSCl, Et_3N, 4-DMAP, CH_2Cl_2, 47% for **22** and 26% for **23**; (h) $NaBH_4$, $CeCl_3 \cdot 7H_2O$, MeOH, −18 °C, 77%; (i) Ac_2O, 4-DMAP, pyridine, 89%; (j) aqueous HCl, THF, quantitative; (k) same as h, 38% and its diastereomer 28%; (l) same as i, 93%; (m) same as j, 98%; (n) MnO_2, CH_2Cl_2, 89%.

butylammonium fluoride afforded a primary alcohol derivative **19**. The Dess−Martin oxidation[14] of **19** gave the aldehyde, which was allowed to react with the 2-lithiated furan to produce the furfuryl alcohols **2** and *epi*-**2** as an inseparable 3:2 diastereomeric mixture regarding the carbinol center. The desired diastereomer **2** was obtained as a sole product by an oxidation−reduction procedure. Thus, the mixture of **2** and *epi*-**2** was oxidized with manganese dioxide, and the resulting ketone **20** was reduced with L-Selectride, providing **2** stereoselectively.[15] It is well recognized that the rearrangement of furfuryl alcohols to pyranones occurs under oxidation conditions, and a number of procedures for this purpose have been reported.[5] We chose a vanadium-catalyzed peroxide addition followed by a rearrangement reaction,[16] which was anticipated to prevent the oxidation of the diene part on the eight-membered ring. As expected, the chemoselective oxidation was realized by the treatment of **2** with *tert*-butyl hydroperoxide in the presence of a catalytic amount of vanadyl acetylacetonate ($VO(acac)_2$), eventually providing **21** as a 2:1 hemiacetal mixture. The hemiacetal hydroxyl groups in mixture **21** were protected as *tert*-butyldimethylsilyl (TBS) ethers, giving a 47% yield of α-isomer **22** and a 26% yield of *β*-isomer **23**.[17] The α-silyl ether **22** was subjected to Luche reduction conditions[18] to afford allylic alcohol **24** with a high level of diastereoselectivity. Acetylation of **24** gave **25**, the stereochemistry of which was confirmed by ^1H NMR analysis, including a NOE experiment.[19] Acid hydrolysis of the TBS group in **25** with dilute HCl provided lactol **26**. On the other hand, the minor silyl ether **23** was also transformed into **26** by the same reaction sequence used for the conversion of **22** to **26**. In this case, the stereoselectivity of the Luche reduction was less satisfactory (dr = 1.3:1). Finally, the oxidation of **26** provided (±)-mycoepoxydiene (**1**), the spectroscopic data (^1H and ^{13}C NMR) of which were well matched with those reported for natural **1**.[1]

In conclusion, we have achieved the first total synthesis of (±)-mycoepoxydiene (**1**) in 24 steps with a 1.6% overall yield from the Diels−Alder adduct of furan and maleic anhydride. The present synthesis demonstrates the efficiency of the RCM approach to access the oxygen-bridged bicyclooctene skeleton. Current efforts in our laboratory are directed at the development of the asymmetric synthesis of mycoepoxydiene.

Supporting Information Available: Experimental procedures and spectroscopic characterization (^1H and ^{13}C NMR, IR, and HRMS) of all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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(13) For previous reports on the synthesis of substituted 9-oxabicyclo-[4.2.1]nona-2,4-diene derivatives, see: (a) Alvarez, E.; Díaz, M. T.; Pérez, R.; Martín, J. D. *Tetrahedron Lett.* **1991**, *32*, 2241−2244. (b) Alvarez, E.; Díaz, M. T.; Pérez, R.; Ravelo, J. L.; Regueiro, A.; Vera, J. A.; Zurita, D.; Martín, J. D. *J. Org. Chem.* **1994**, *59*, 2848−2876. (c) Huang, D.-J.; Rayabarapu, D. K.; Li, L.-P.; Sambaiah, T.; Cheng, C.-H. *Chem. Eur. J.* **2000**, *6*, 3706−3713.

(14) (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.

(15) We did not confirm the configuration of the introduced stereogenic center in **2** at this stage.

(16) Ho, T.-L.; Sapp, S. G. *Synth. Commun.* **1983**, *13*, 207−211.

(17) The configuration of the hemiacetal carbon in the major diastereomer **22** as depicted was determined after transformation of **22** into **25**.

(18) Gemal, A. L.; Luche, J.-L. *J. Am. Chem. Soc.* **1981**, *103*, 5454−5459.

(19) As shown in Scheme 4, significant signal enhancements at H1 (14%), H4 (7.6%), and H7 (6.9%) were observed when H5 was irradiated. The lack of signal enhancement at H6 as well as the 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. Therefore, the stereochemistry of **25** was determined as depicted.