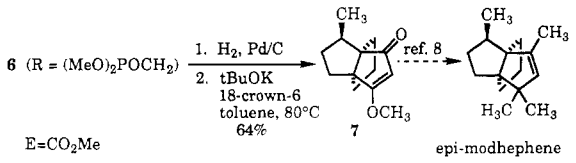
Scheme II



concentrated sulfuric acid at 0 °C generated a diketone from a Michael addition reaction. This diketone could be cyclized to **4** in 77% yield by treatment with concentrated sulfuric acid at ambient temperature.[7] The reaction of **4** with the lithium enolate of acetophenone (−78 °C to 0 °C) furnished diketone **6** in 41% yield. The reaction of **4** with $(MeO)_2POCH_2Li$ afforded keto phosphonate **6** in 70% yield. The reaction of **4** with MeMgBr in ether at 0 °C produced the unrearranged tertiary alcohol as a mixture of stereoisomers.

The bicyclic compound **6** contains two of the three rings of modhephene, a novel terpene (Scheme II). Unexpectedly, catalytic hydrogenation of **6** produced one isomer by reduction from the more hindered endo face. Cyclization with potassium *tert*-butoxide and 18-crown-6 at 80 °C in toluene afforded **7**, an intermediate in the Mundy syntheses of *epi*-modhephene,[8] in 64% yield. Since **7** was converted by Mundy into *epi*-modhephene, this represents a formal synthesis of *epi*-modhephene. Compound **7** is available from **2** in 34% overall yield.

This rearrangement reaction is compatible with a variety of functional groups. The synthesis of an advanced intermediate in the Mundy synthesis of *epi*-modhephene confirms the structural assignments of the rearrangement products.[9] The research described herein opens up a new pathway by which bicyclo[3.3.0]octanes and their 3-aza counterparts can be constructed.

Registry No. (±)-**1**, 98263-13-9; **2**, 30132-23-1; (±)-**3**, 128164-63-6; (±)-**4**, 128164-64-7; (±)-**5** (R = (1-cyclohexenylcarbonyl)methyl), 128164-65-8; (±)-**5** (R = $PhCOCH_2$), 128164-66-9; (±)-**5** (R = Ph), 128164-67-0; (±)-**5** (R = Me), 128164-68-1; (±)-**6** (R = $PhCOCH_2$), 128164-69-2; (±)-**6** (R = $(MeO)_2P(O)CH_2$, 128164-70-5; (±)-**7**, 127419-76-5; $PhCOCH_2Li$, 55905-98-1; PhLi, 591-51-5; MeLi, 917-54-4; $(MeO)_2P(O)CH_2Li$, 34939-91-8; 1-acetylcyclohexene lithium enolate, 128164-71-6; (±)-*epi*-modhephene, 76739-65-6.

Supplementary Material Available: Experimental procedure for **4** and spectral data for **5** and **6** (2 pages). Ordering information is given on any current masthead page.

(7) For a related procedure, see: Heathcock, C. H.; Ellis, J. E.; McMurry, J. E.; Coppolino, A. *Tetrahedron Lett.* **1971**, 4995.

(8) For comparison with authentic spectra, see: Mundy, B. P.; Wilkening, D.; Lipkowitz, K. B. *J. Org. Chem.* **1985**, *50*, 5727.

(9) Jasperse, C. P.; Curran, D. P. *J. Am. Chem. Soc.* **1990**, *112*, 5601-5608. Explanation of this unusual reduction reaction will be provided in the full paper. Reduction of **6** with $[Ir(COD)(PCy_3)py]PF_6$ and H_2 followed by cyclization (KH, PhH) and alkylative transposition (MeLi, HCl) afforded Curran's intermediate.

High Diastereofacial Differentiation in Osmium Tetraoxide Catalyzed Dihydroxylation of Acyclic Bis-allylic Compounds

Seiki Saito,* Yasuhisa Morikawa, and Toshio Moriwake*

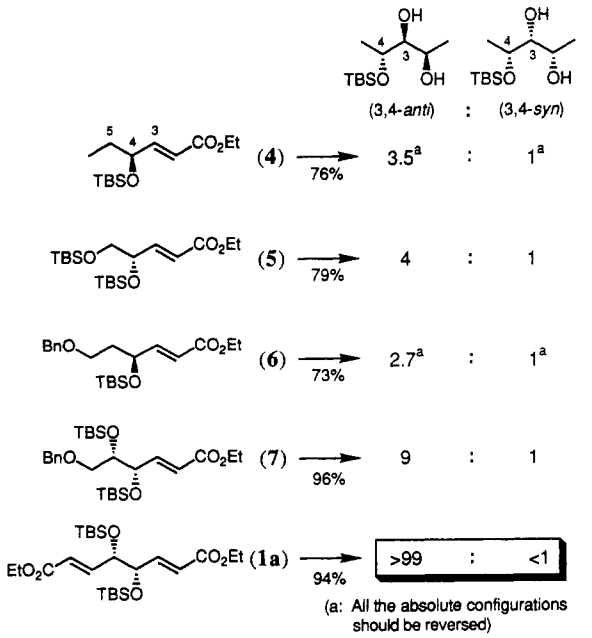
Department of Applied Chemistry, Faculty of Engineering, Okayama University, Tsushima, Okayama, Japan 700

Received June 8, 1990

Summary: Bis-allylic compounds such as diethyl (4*S*,5*S*)-4,5-bis((*tert*-butyldimethylsilyl)oxy)-2,6-octadienedioate (**1a**) exhibit very high diastereoselection in osmium tetraoxide catalyzed dihydroxylation; a particular ground-state conformation is proposed to be responsible.

Osmium tetraoxide catalyzed oxidations of carbon–carbon double bonds have proven to be very useful for introducing vicinal dihydroxyl groups onto 1,2-disubstituted olefins bearing an allylic oxygen stereocenter in a stereochemically predictable manner.[1] Kishi has proposed a useful empirical model based on a reactant-like eclipsed transition state.[1d] However, the diastereomeric excesses observed in these processes vary considerably from sub-

Scheme I



(1) (a) Cha, J. K.; Christ, W. J.; Kishi, Y. *Tetrahedron Lett.* **1983**, *24*, 3943-3946. (b) Christ, W. J.; Cha, J. K.; Kishi, Y. *Tetrahedron Lett.* **1983**, *24*, 3947-3950. (c) Stork, G.; Kahn, M. *Tetrahedron Lett.* **1983**, *24*, 3951-3954. (d) Cha, J. K.; Christ, W. J.; Kishi, Y. *Tetrahedron* **1984**, *40*, 2247-2255. (e) Hauser, F. M.; Ellenberger, S. R.; Clardy, J. C.; Bass. L. S. *J. Am. Chem. Soc.* **1984**, *106*, 2458-2459. (f) Johnson, C. R.; Barbachyn, M. R. *Ibid.* **1984**, *106*, 2459-2461. (g) Colombo, L.; Gennari, C.; Poli, G.; Scolastico, C.; Munari, S. D. *Tetrahedron Lett.* **1985**, *26*, 5459-5462. (h) Solladié, G.; Frêchou, C.; Demailly, G. *Ibid.* **1986**, *27*, 2867-2870. (i) Vedejs, E.; McClure, C. K. *J. Am. Chem. Soc.* **1986**, *108*, 1094-1096. (j) Solladié, G.; Hutt, J.; Frêchou, C. *Ibid.* **1987**, *28*, 61-64. (k) Annunziata, R.; Cinquini, M.; Cozzi, F. *Ibid.* **1987**, *28*, 3139-3142. (l) Fleming, I.; Sarker, A. K.; Thomas, A. P. *J. Chem. Soc., Chem. Commun.* **1987**, 157-159. (m) DeNinno, M. P.; Danishefsky, S. J.; Schulte, G. *J. Am. Chem. Soc.* **1988**, *110*, 3925-3929. (n) Vedejs, E.; Dent, W. H. III *J. Am. Chem. Soc.* **1989**, *111*, 6861-6862. (o) Evans, D. A.; Kaldor, S. W. *J. Org. Chem.* **1990**, *55*, 1698-1700. (p) for a review, see: Nakajima, M.; Tomioka, K.; Koga, K. *J. Synth. Org. Chem. Jpn.* **1989**, *47*, 878-888.

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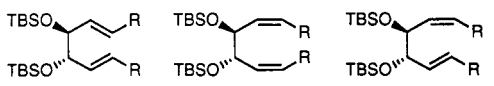
strate to substrate.[1] Encouraged by our recent success in the asymmetric Michael process of related compounds,[2] we were intrigued with the possibility of achieving high differentiation of diastereo π(C=C) faces of acyclic allylic olefins in dihydroxylations catalyzed by osmium tetraoxide.



1a-c **2b,c** **3b,c**

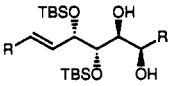
(a: R=CO_2Et, b: R=CH_2OAc, c: R=CH_2OBn)

We have investigated bis-allylic compounds **1**,[2] **2**,[3] and **3**[4] bearing vicinal (*tert*-butyldimethylsilyl)oxy (TBSO) substituents which play an important role in controlling the rotational isomer population.[2] One important consequence is that the two double bonds mutually shield two diastereofaces in a topological sense, thereby leaving only the other two diastereofaces available for osmium attack.[2] In fact, the reaction of osmium tetraoxide with these dienes has provided extremely high diastereomeric excesses (>99%) for both olefinic moieties irrespective of its geometry.

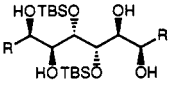
The preliminary results (Scheme I) with regard to the diastereoselectivity of osmylation [OsO_4 (5 mol %)/*N*-methylmorpholine *N*-oxide (NMO: 2 equiv)/acetone–H_2O (5:1)/25 °C][5] executed for **4–7**[6] provide a marked contrast to the bis-allylic substrate **1a**.

The ability of the allylic TBSO group to differentiate the neighboring π-faces in this reaction has been estimated to be 3.5:1 based on the diastereoselectivity observed for **4**. Although a second TBSO group (**5**) or (benzyloxy)-methyl group (**6**) at C-5 had virtually no effect on selectivity, the introduction of both groups at C-5 (**7**) doubled the anti/syn ratio (9:1). Furthermore, by replacing the (benzyloxy)methyl group with the same *E*-enoate functionality (**1a**), the diastereomeric excess reached >99:1 in favor of **8a** as verified by NMR diagnosis (500 MHz) and chemical correlation.[7] Thus, bis-allylic dienes such as **1a** are promising substrates for high diastereoselection in osmium tetraoxide hydroxylations.

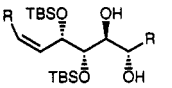
The high diastereoselectivity exhibited by **1a** is also observed with the related bis-allylic compounds **1b–c**, **2**, and **3**. Osmylation of *Z,Z* isomer **2** afforded exclusively the 2,3-*anti*-3,4-*anti* product (**9**)[7] under the identical conditions. Although *E,Z* isomer **3** led to a mixture of regioisomers stemming from competitive oxidation toward the *E* and *Z*-olefinic moieties in a ratio 13 (**10b**):1, the diastereoselection with regard to each product was again extremely high.[7] Furthermore, when 4 molar equiv of NMO were employed, the osmylation of **1**, **2**, and **3** afforded 2,3,6,7-tetrahydroxylated products **11**,[8] **12**,[8] and **13**,[9] respectively, as single isomers. Thus, the double hydroxylation of these bis-allylic substrates[10] is a promising strategy for acyclic synthesis of six contiguous oxygen-bearing chiral centers.



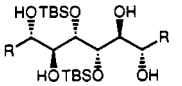
8a: R = CO_2Et (94%)
8b: R = CH_2OAc (87%)



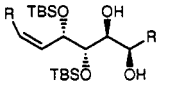
11a: R = CO_2Et (88%)
11b: R = CH_2OAc (93%)
11c: R = CH_2OBn (89%)



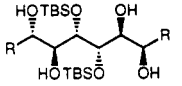
9b: R = CH_2OAc (79%)
9c: R = CH_2OBn (72%)



12b: R = CH_2OAc (72%)
12c: R = CH_2OBn (80%)



10b: R = CH_2OAc (68%)



13b: R = CH_2OAc (84%)
13c: R = CH_2OBn (84%)

The high diastereomeric excesses observed for **1**, **2**, and **3** require a satisfactory explanation. We have proposed that the particular ground-state conformation, for instance C, must be responsible for the stereoselectivity of asymmetric Michael reactions.[11] The distinct NOE (2.7%) observed between the C-3 and C-6 olefinic protons of **3b** provides clear-cut physical evidence supporting this interpretation. These protons can be in close proximity only in the conformation **3b**(C). Substrates **1** or **2**, albeit not amenable to NOE experiment because of their axially dissymmetric nature, should likewise exist in a conformation A or B.

In addition, chemical evidence supporting conformation A has been obtained. While **5** afforded the corresponding bromohydrin in 85% yield on treatment with NBS in MeCN–H_2O (25 °C, 40 h), the reaction of **1a** did not proceed to an any extent under the same conditions, unchanged **1a** being quantitatively recovered. We can readily understand that a bromonium ion, even if it is generated from **1a**, would never allow an external nucleophile to attack the rear side because it is effectively shielded by the remaining allylic moiety see conformation A). Although there exist other two possible conformations such as A′ and A″ which may lead to a 3,4-syn isomer (Scheme I), these apparently suffer from severe steric congestion.

The high diastereoselectivity of the second osmylation clearly indicates that the conformation of the olefinic moieties illustrated as A, B, or C must be retained after

(2) Saito, S.; Hirohara, Y.; Narahara, O.; Moriwake, T. *J. Am. Chem. Soc.* **1989**, *111*, 4533–4535.

(3) Prepared from the corresponding bis-enoate (Krief, A.; Dumont, W. *Tetrahedron Lett.* **1988**, *29*, 1083–1086) through a series of routine reactions.

(4) Prepared from 1-*O*-TBS-2,3-*O*-isopropylidene-L-threitol [(a) Hungerbühler, E.; Seebach, D. *Helv. Chim. Acta* **1981**, *64*, 687–702) through a series of reactions involving (i) Swern oxidation, (ii) Wadsworth–Emmons condensation [(b) Still, W. C.; Gennari, C. *Tetrahedron Lett.* **1983**, *24*, 4405–4408], (iii) TBS-deprotection and *Z* isomer isolation, (iv) Swern oxidation, and (v) Wadsworth–Emmons condensation (ethyl diisopropylphophonoacetate).

(5) (a) VanRheenen, V.; Kelly, R. C.; Cha, D. Y. *Tetrahedron Lett.* **1976**, 1973–1976. (b) Ray, R.; Mateson, D. S. *Ibid.* **1980**, *21*, 449–450.

(6) The preparation of **4–7**:**4** (ref 1c), **5** from commercial (*R*)-1,2-*O*-isopropylideneglycerol, and **6** and **7** from diethyl (*S*)-maleate and 1-*O*-benzyl-2,3-*O*-isopropylidene-L-threitol (4a), respectively.

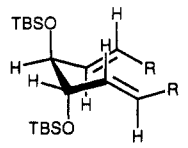
(7) See ref 8.

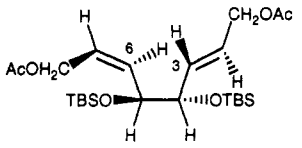
(8) The absolute configurations were determined by chemical correlations of 1-*O*-benzyl-2,3-*O*-isopropylidene-D-threitol derived from, for instance, 11c through (i) 2,2-dimethoxypropane/acetone/*p*-TsOH, (ii) $(n\text{-Bu})_4NF$/THF, (iii) $Pb(OAc)_4$/THF, (iv) $NaBH_4/Na_2CO_3$/THF (56% overall yield) ($[\alpha]^{26}_D$ −9.31° (*c* 1.44, $CHCl_3$)), and of (−)-1-*O*-benzyl-2,3-*O*-isopropylideneerythritol (62% overall yield) derived from **13c** in the same way as just mentioned above ($[\alpha]^{26}_D$ −3.82° (*c* 2.20, EtOH)) with authentic samples [lit. $[\alpha]^{26}_D$ −8.0° (*c* 5.82, $CHCl_3$) for the D-threitol derivative (4a) and $[\alpha]^{26}_D$ −3.7° (*c* 2.31, EtOH) for the erythritol derivative (98 % ee) (Katsuki, K.; Lee, A. W. M.; Ma, P.; Martin, V. S.; Masamune, S.; Sharpless, K. B.; Tuddenham, D.; Walker, F. J. *J. Org. Chem.* **1982**, *47*, 1373–1378).

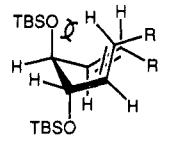
(9) Led to an exact 1:1 mixture of D-threitol (see ref 8) and (−)-erythritol (see ref 8) derivatives through the four-step sequence shown in ref 8 as confirmed by a capillary GLC analysis.

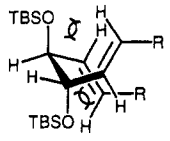
(10) For a recent two-directional chain synthesis employing a bis-allylic system, see: (a) Schreiber, S. L.; Schreiber, T. S.; Smith, D. B. *J. Am. Chem. Soc.* **1987**, *109*, 1525–1527. (b) Schreiber, S. L.; Goulet, M. T.; Schulte, G. *J. Am. Chem. Soc.* **1987**, *109*, 4718–4720.

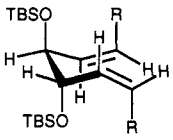
(11) For discussion about this point, see ref 2.

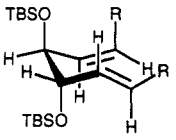

A


3b(C)

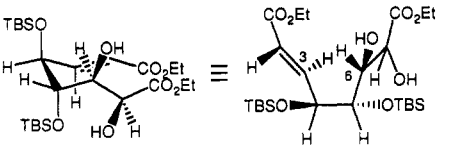

A'


A"


B


C

the initial introduction of the 2,3-dihydroxyl functionality. We tested this point by an NOE experiment. A strong NOE (5%) was again observed for the C-3 proton of **8a** when the C-6 proton was irradiated. Thus conformational assignment of **8a** as **8a**(A) is justified. This is obviously crucial for high discrimination by osmium tetraoxide in the second oxidation leading to **11a**, and this situation has proven also to be the case for both **9** and **10**.


8a(A)

All facts obtained in this work are consistent with the proposal that osmylation of bis-allylic dienes **1**, **2**, or **3** proceeds by way of conformers A, B, or C, respectively. Stereoelectronic π-facial bias imposed by the allylic TBSO group (Kishi's model)[1d] seems to be insufficient to explain the dramatic change in diastereoselection from **4**–**7** to **1a** (Scheme I), although this model does predict the diastereomeric outcome of each reaction. The exceptionally high % de observed for **1**, **2**, and **3** are not satisfactorily accounted for by other proposed models.[1i,n,12]

Acknowledgment. We thank to The SC-NMR Laboratory of Okayama University for the high-field (500-MHz) NMR experiments. We deeply appreciate the financial support by a Grant-in-Aid for Scientific Research from the Ministry of Education, Science, and Culture, Japan.

Supplementary Material Available: Representative syntheses, physical data (^{1}H NMR, ^{13}C NMR, IR, $[\alpha]_D$, and elemental analyses), and NMR spectra (20 pages). Ordering information is given on any current masthead page.

(12) (a) Houk, K. N.; Paddon-Row, M. N.; Randan, N. G.; Wu, Y.-D.; Brown, F. K.; Spellmeyer, D. C.; Metz, J. T.; Li, Y.; Loncharich, R. J. *Science* **1986**, *231*, 1108. (b) Houk, K. N.; Duh, H.-Y.; Wu, Y.-D.; Moses, S. R. *J. Am. Chem. Soc.* **1986**, *108*, 2754.

Preparation of Bicyclo[5.3.0]decan-1-ols from the Tandem Anionic Oxy-Cope Rearrangement/Allylsilane Cyclization of 1,2-Divinylcyclohexanols

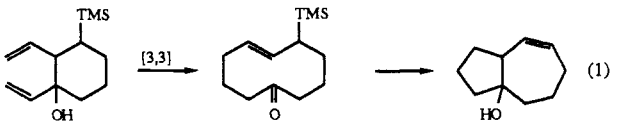
Li Jisheng, Teresa Gallardo, and James B. White*

Department of Chemistry, Box 19065, The University of Texas at Arlington, Arlington, Texas 76019

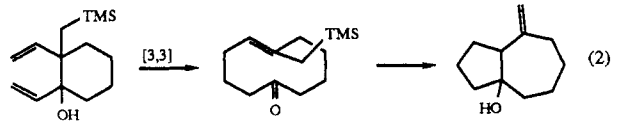
Received July 10, 1990

Summary: Intramolecular cyclization of the allylsilanes produced from anionic oxy-Cope rearrangement of 1,2-divinylcyclohexanols led to hydroazulenols with the cis ring fusion.

A number of natural products of biological interest, such as the tumor-promoting phorbol esters[1] and the neurotoxic grayanotoxins,[2] contain as part of their structure, a hydroazulene with a bridgehead hydroxyl group. We envisioned a two-step process for converting appropriately substituted cyclohexanols into hydroazulenols, which is illustrated in eqs 1 and 2. Anionic oxy-Cope rearrangement of divinylcyclohexanols **1a–b** is well precedented[3] and leads to the cyclodecenones **2a–b**. As a consequence of the rearrangement, an allylsilane is generated in **2a–b**, which, if capable of intramolecular cyclization[4] with the ketone,


(1)

1a **2a** **3a**


(2)

1b **2b** **3b**

leads to the bicyclo[5.3.0]decan-1-ols **3a–b**. We report herein our preliminary investigation into this synthetic methodology.[5]

The 1,2-divinylcyclohexanols **1a–b** were prepared as shown in Scheme I. Silyl enol ether **4**[6] was converted into

(1) For a lead reference on phorbol esters and structurally related compounds, see: Wender, P. A.; Lee, H. Y.; Wilhelm, R. S.; Williams, P. D. *J. Am. Chem. Soc.* **1989**, *111*, 8954-7.

(2) Codding, P. W. *J. Am. Chem. Soc.* **1984**, *106*, 7905-9.

(3) (a) Still, W. C. *J. Am. Chem. Soc.* **1977**, *99*, 4186-7. (b) Still, W. C. *J. Am. Chem. Soc.* **1979**, *101*, 2493-5. (c) Clive, D. L. J.; Russell, C. G.; Suri, S. C. *J. Org. Chem.* **1982**, *47*, 1632-41.

(4) For a recent review on intramolecular allylsilane cyclizations, see: Schinzer, D. *Synthesis* **1988**, 263-73.

(5) An alternative approach to hydroazulenes involving anionic oxy-Cope rearrangement of divinylcyclohexanols followed by intramolecular alkylation of the intermediate enolate has recently been described. For examples, see: (a) Sworin, M.; Lin, K.-C. *J. Am. Chem. Soc.* **1989**, *111*, 1815-25. (b) Paquette, L. A.; Reagan, J.; Schreiber, S. L.; Teleha, C. A. *J. Am. Chem. Soc.* **1989**, *111*, 2331-2. (c) Paquette, L. A.; Shi, Y.-J. *J. Org. Chem.* **1989**, *54*, 5205-7.

0022-3263/90/1955-5426$02.50/0