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Exploratory Studies Aimed at a Synthesis of Vinigrol. 2. Attempts to Exploit Ring-Closing Metathesis for Construction of the Central Cyclooctane Belt

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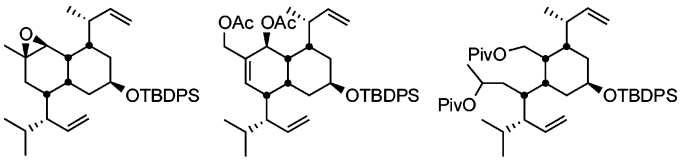
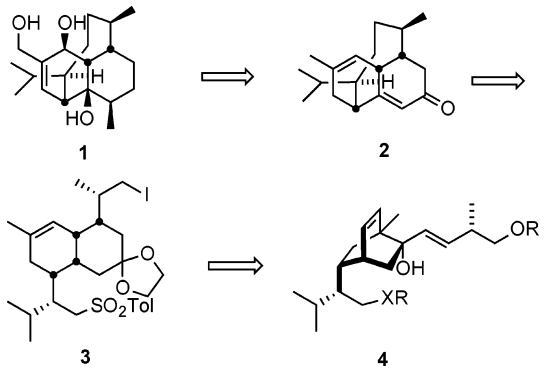


All three compounds are not responsive to ring closing metathesis.

A program directed to the possible adaptation of ring closing metathesis to a total synthesis of vinigrol is described. With a convenient route to intermediates of general type **3** available from a prior investigation, several candidate substrates were prepared. These included the epoxy dienes **10** and **22**, the diacetoxy triene **42**, and the heavily functionalized cyclohexane **48**. The central issue of this approach was to convey a maximum degree of conformational flexibility to these functionalized intermediates, such that the olefinic termini of the side chains could enter into intramolecular carbon−carbon bond formation. In no example was ring closure observed to operate. Instead, the strategically placed π-bonds were seen to migrate internally to the chain in select examples. Although the pivotal transformations failed, the deployment of a number of useful stereocontrolled reactions has ultimately resulted in the preparation of heavily substituted *cis*-decalins.

Vinigrol (**1**), a metabolite of *Virgaria nigra*, was shown to possess unprecedented structural features on the basis of a crystallographic determination.[1] Early interest in this substance was additionally fueled by its unusually promising antihypertensive and platelet aggregation inhibitory properties.[2] The later discovery of its role as a tumor necrosis factor antagonist[3] has also been contributory to heightened synthetic attention,[4−6] including our projection of a possible enantioselective total synthesis.[7]

SCHEME 1



Detailed in part 1 of this series was a retrosynthetic plan to arrive at the potential precursor **2** by means of the S_N2 intramolecular cyclization of iodo sulfone **3** (Scheme 1). While arrival at **3** via the oxyanionic-accelerated [3,3]-sigmatropic rearrangement of **4** efficiently set the four vicinal methine hydrogens in the targeted all-cis arrangement, no subsequent ring closure to establish the ansa bridge in the tricyclic product was accomplished. The recalcitrance of **3** toward generation of the eight-

(1) Uchida, I.; Ando, T.; Fukami, N.; Yoshida, K.; Hashimoto, M.; Tada, T.; Koda, S.; Morimoto, Y. *J. Org. Chem.* **1987**, *52*, 5292.
(2) (a) Ando, T.; Tsurumi, Y.; Ohata, N.; Uchida, I.; Yoshida, K.; Okuhara, M. *J. Antibiot.* **1988**, *41*, 25. (b) Ando, T.; Yoshida, K.; Okuhara, M. *J. Antibiot.* **1988**, *41*, 31.
(3) Norris, D. B.; Depledge, P.; Jackson, A. P. PCT Int. Appl. WO 91 07 953; *Chem. Abstr.* **1991**, *115*, 64776h.
(4) (a) Devaux, J.-F.; Hanna, I.; Lallemand, J.-Y.; Prangé, T. *J. Org. Chem.* **1993**, *58*, 2349. (b) Devaux, J.-F.; Fraisse, P.; Hanna, I.; Lallemand, J.-Y. *Tetrahedron Lett.* **1995**, *36*, 9471. (c) Devaux, J.-F.; Hanna, I.; Lallemand, J.-Y. *J. Org. Chem.* **1997**, *62*, 5062. (d) Gentric, L.; Hanna, I.; Ricard, L. *Org. Lett.* **2003**, *5*, 1139.
(5) (a) Kito, M.; Sakai, T.; Haruta, N.; Shirahama, H.; Matsuda, F. *Synlett* **1996**, 1057. (b) Matsuda, F.; Kito, M.; Sakai, T.; Okada, N.; Miyashita, M.; Shirahama, H. *Tetrahedron* **1999**, *55*, 14369.
(6) Mehta, G.; Subba Reddy, K. *Synlett* **1996**, 625.
(7) Paquette, L. A.; Guevel, R.; Sakamoto, S.; Kim, I. H.; Crawford, J. *J. Org. Chem.* **2003**, *68*, 6096.

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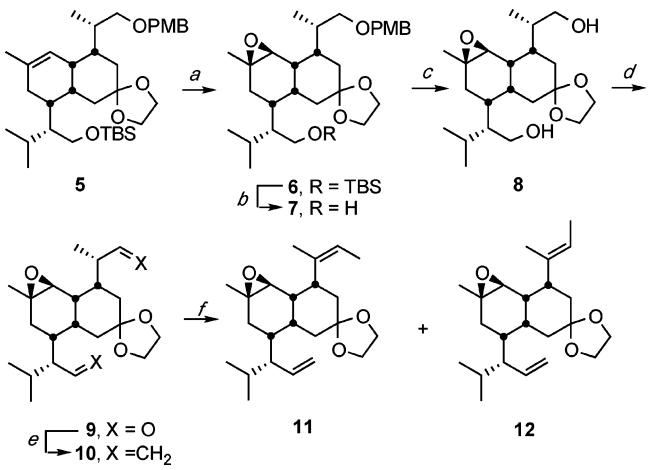
SCHEME 2[a]



[a] Reagents and Conditions: (a) *m*-CPBA, Na_2HPO_4, CH_2Cl_2 (99%); (b) TBAF, THF, rt (quant); (c) DDQ, CH_2Cl_2, H_2O (quant); (d) $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2, −78 → −40 °C (89%); (e) $Ph_3P{=}CH_2$, THF, 0 °C (77%); (f) Grubbs catalyst, C_6H_6, reflux (44% of **11** and 36% of **12**).

membered ring was attributed to conformational factors that inhibit attainment of the proper S_N2 reaction trajectory.[7] This particular methodology requires not only spatial proximity of the reacting centers but also their strictly defined orientation. A preferred protocol having less stringent entropic demands should, on this basis, serve better as a candidate for the intended mesocyclic carbon−carbon bond formation. In light of the Chauvin mechanism for ring closing metathesis (RCM),[8] which stresses the significance of metallocyclobutane and metallocarbene intermediates, the prospects for intramolecular formation of a cyclooctene double bond attracted our attention. This choice was not without complications. The difficulty arises from the fact that reliance must be placed on adequate conformational flexibility within the cis-fused decalin core.

In this paper, we delineate three attempts to harness this particular power reaction for the purpose of accessing vinigrol (**1**).

Results and Discussion

Consequences of Preliminary Epoxidation. For the RCM to proceed as planned, the endocyclic double bond in **5**[7] was initially protected to avoid its possible participation. These considerations led us to advance by means of the stereocontrolled epoxidation of acetal **5** (Scheme 2). This transformation was expedient in that those stereochemical issues associated with reduction of the carbonyl group were effectively skirted. By proceeding in this direction, however, we were aware that potential awkwardess arising from added steric congestion could well manifest itself. Diene **10** was ultimately prepared from **6** by sequential deprotection of the hydroxyl functionalities, Swern oxidation, and 2-fold methylenation of the resulting dialdehyde **9** by way of Wittig chemistry. Relevantly, no epimerization at the allylic sites was revealed by high-field ^1H NMR analysis. Heating **10** with the first-generation Grubbs catalyst[9] in refluxing chloroform or benzene gave no sign of reaction. When the more reactive second-generation ruthenium catalyst[10] was deployed instead, processing in hot benzene was found to induce only double-bond migration as in **11** and **12**. Related isomerizations have been previously reported.[11] In the present context, its operation suggests that the intended internal coupling is kinetically inhibited. A change in the functionalization pattern was clearly mandated, and we therefore undertook to explore that facet of Scheme 1 featuring precursors that have a bulky substituent in β-orientation at C-7. Doing so was expected to facilitate adoption of those conformational changes potentially more conducive to the cyclization reaction.

The practicalities associated with diol **13**, available via a two-step deprotection of **5**, allowed significant sums of material to be brought forward by way of the doubly protected acetal **14**. Acid hydrolysis to unmask the ketone carbonyl made possible the subsequent determination that attack during sodium borohydride reduction proceeds preferentially from the more open β-surface. The requisite inversion of configuration as **15** to **16** was accomplished using an improved variant of the Mitsunobu reaction.[12] The free hydroxyl group in **16**, cleanly liberated by exposure of **17** to lithium hydroxide in aqueous THF, was protected as a *tert*-butyldiphenylsilyl ether, and the primary hydroxyls were liberated by the action of DDQ to furnish **20**. The information garnered earlier in connection with the preparation of **10** proved to be transmittable to the elaboration of **22**. We now focused on the reactivity of **22** under RCM conditions. In refluxing CH_2Cl_2 as the metathesis medium, neither Grubbs catalyst promoted a chemical change. In agreement with the previous observations, use of higher temperatures (e.g., benzene at reflux) led to migration of the double bond(s). Mass spectrometric analysis of these reaction mixtures demonstrated unmistakably that no **23** had been generated (Scheme 3).

Migration of the Double Bond in the Octalin Core. In light of the preceding developments, we next considered the possibility of temporarily migrating the double bond in several intermediates from its original $\Delta^{3,4}$ location to the neighboring $\Delta^{2,3}$ site. As reflected in the model systems **A** and **B** (Figure 1), this relocation was to be counted on for increased conformational flexibility, such that the two side chains might be projected axially with greater facility as suggested by MM3 calculations.

Three approaches to structural modification of the left-hand domain were addressed in turn. The first-generation pathway was designed to involve 2-fold deployment of the epoxide → allyl alcohol rearrangement under basic conditions (Scheme 4). To evaluate this technology relative to the case at hand, resources were directed to the preparation of **24**, available from the disilylation of **19**.

(8) (a) Harrison, J.-L.; Chauvin, Y. *Makromol. Chem.* **1971**, *141*, 161. (b) Soufflet, J.-P.; Commereuc, D.; Chauvin, Y. *Compt. Rend. Acad. Sci. Ser. C* **1973**, *276*, 169. (c) Chauvin, Y.; Commereuc, D.; Zaborowski, G. *Makromol. Chem.* **1978**, *179*, 1285.

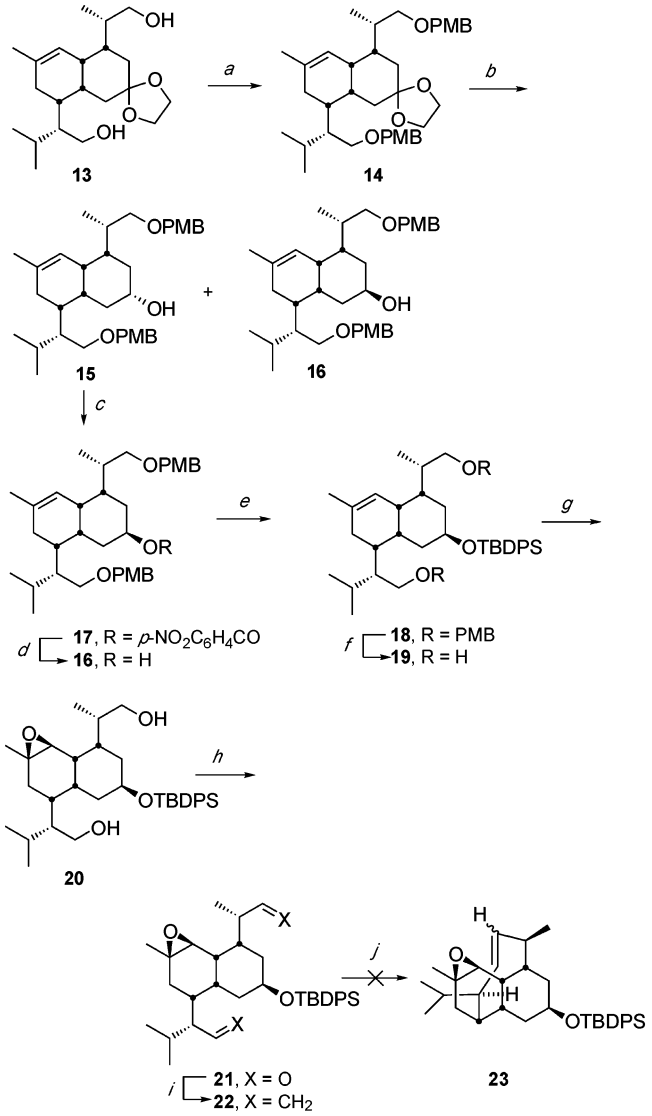
(9) Ulman, M.; Grubbs, R. H. *J. Org. Chem.* **1999**, *64*, 7202 and references therein.

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

(11) Corey, E. J.; Guzman-Perez, A. *Angew. Chem., Int. Ed.* **1998**, *37*, 388.

(12) Dodge, J. A.; Trujillo, J. I.; Presnell, M. *J. Org. Chem.* **1994**, *59*, 234.

SCHEME 3[a]



[a] Reagents and conditions: (a) PMBCl (2.0 equiv), NaH, DMF (43% for **14**, 44% for the monoprotected alcohol); (b) 1.0 M HCl, acetone; $NaBH_4$, EtOH (78% for **15**, 20% for **16**); (c) *p*-nitrobenzoic acid, PPh_3, DEAD, THF (99%); (d) LiOH, H_2O, THF (98%), (e) TBDPSCl, imidazole, DMF; (f) DDQ, H_2O, CH_2Cl_2 (84% for two steps); (g) *m*-CPBA, Na_2HPO_4, CH_2Cl_2 (quant); (h) $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2, −78 → −40 °C (82%); (i)$Ph_3P{=}CH_2$, THF (65%); (j) RCM conditions (see text).

Exposure of **24** to peracid at 0 °C afforded **25**. Treatment of this intermediate with diethylaluminum 2,2,6,6-tetramethylpiperidide (DATMP)[13] led to regioselective formation of **26** in 98% yield. Subsequent vanadium-catalyzed epoxidation[14] gave epoxy alcohol **27** as a single isomer. When conditions were screened for the conversion of **27** to **29**, rearrangement invariably occurred to generate aldehyde **28** instead. The possibility that the proximal free hydroxyl may have redirected the desired isomerization prompted conversion of **27** to its trimethylsilyl ether. However, this compound proved unreactive to the standard conditions, as well as to lithium diisopropylamide in ether.

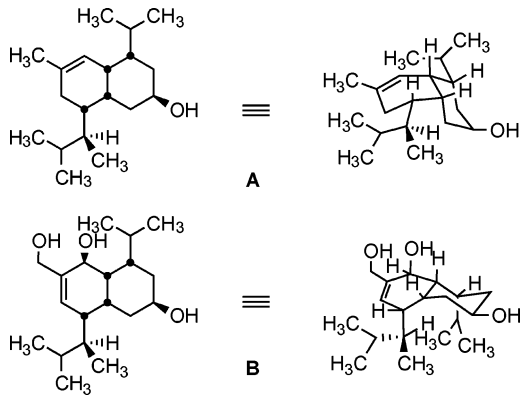
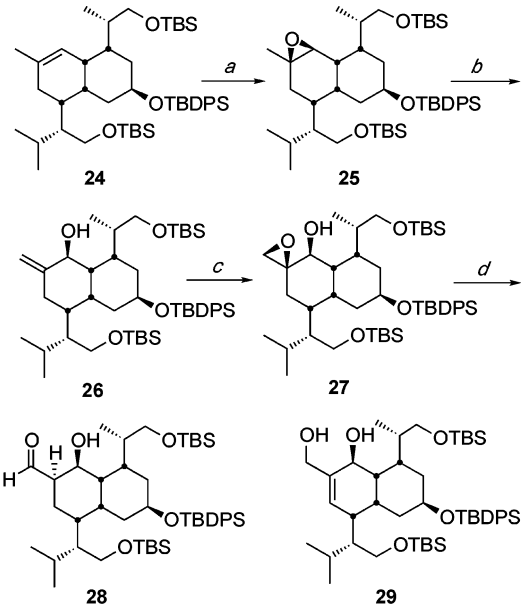


FIGURE 1.

SCHEME 4[a]



[a] *Reagents and Conditions:* (a) *m*CPBA, Na_2HPO_4, CH_2Cl_2, 0 °C (98%); (b) N-AlEt$_2$ (DATMP), C_6H_6, 0 °C (98%); (c) $VO(acac)_2$, *t*-BuOOH, C_6H_6 (100%); (d) DATMP, C_6H_6, 0 °C (36% at 48% conv).

At this juncture, dehydration of a suitable tertiary carbinol became our next objective. Initial efforts to set the stage for this eventuality explored the feasibility of oxirane ring opening in **27** with potassium acetate and 18-crown-6 in DMF at 100 °C.[15] These conditions gave rise to the chromatographically separable diastereomers **30** and **31** in 52% and 12% yield, respectively (Scheme 5). A considerable enhancement in efficiency was realized when recourse was made alternatively to sodium acetate in 2-methoxyethanol and water.[16] Selective protection of the primary and secondary hydroxyl groups in **30** was now mandated. The use of acetic anhydride in pyridine[17]

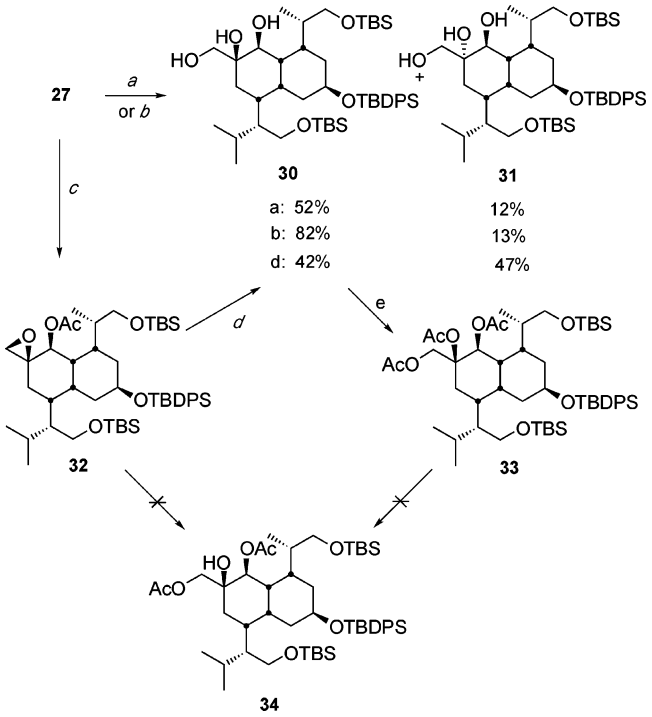
(13) Yasuda, A.; Tanaka, S.; Oshima, K.; Yamamoto, H.; Nozaki, H. *J. Am. Chem. Soc.* **1974**, *96*, 6513.

(14) Sharpless, K. B.; Michaelson, R. C. *J. Am. Chem. Soc.* **1973**, *95*, 6136.

(15) Momose, T.; Setoguchi, M.; Fujita, T.; Tamura, H.; Chida, N. *Chem. Commun.* **2000**, 2237.

(16) (a) Suami, T.; Ogawa, S.; Uematsu, Y.; Suga, A. *Bull. Chem. Soc. Jpn.* **1986**, *59*, 1261. (b) Ogawa, S.; Uematsu, Y.; Yoshida, S.; Sasaki, N.; Suami, T. *J. Carbohydr. Chem.* **1987**, *6*, 471.

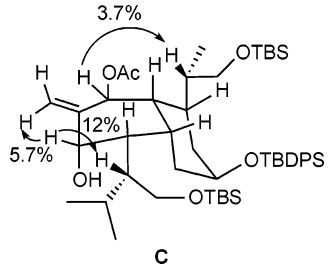
SCHEME 5[a]



[a] Reagents and conditions: (a) KOAc, 18-cr-6, DMF, 100 °C; (b) NaOAc, $MeOCH_2CH_2OH$, H_2O, reflux; (c) Ac_2O, DMAP, py (87%); (d) NaOAc, $MeOCH_2CH_2OH$, H_2O, reflux; (e) Ac_2O, DMAP, py, then Ac_2O, DMAP, CH_2Cl_2 (67%).

afforded only products of monoacetylation (primary/secondary = 3:1 by NMR analysis). Submission of this mixture to the action of acetic anhydride and DMAP in CH_2Cl_2 solution led to the exclusive isolation of triacetate **33**. Our inability to uncover a means for generating **34**[18] for projected dehydration studies prompted a shift in emphasis to the third option.

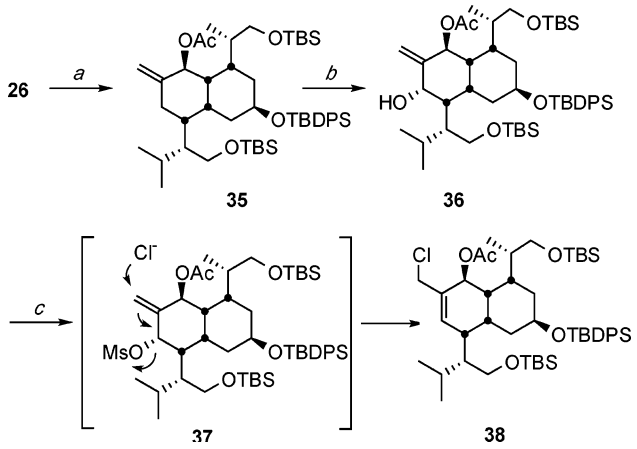
The acetylation of **26** to generate **35** proved to be a reliable first step (Scheme 6). When this intermediate was reacted with selenium dioxide and *tert*-butyl hydroperoxide in CH_2Cl_2 at room temperature,[19] relatively efficient conversion to allyl alcohol **36** was observed. The α-configuration of the newly introduced OH substituent was ascertained on the basis of NOE data as illustrated in **C**. The stage was now set for activation of the system



C

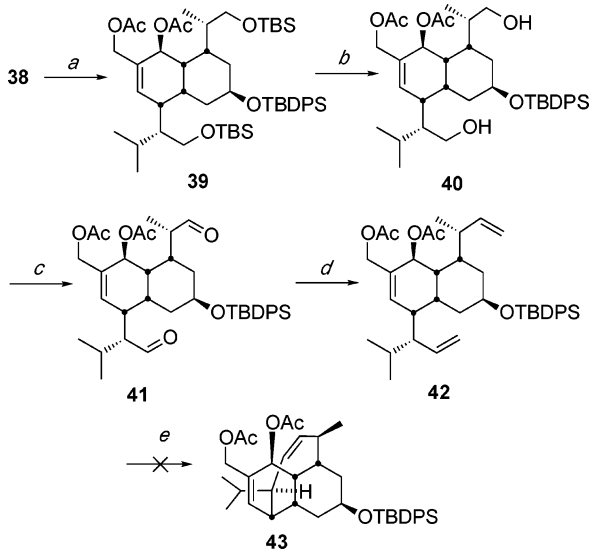
with methanesulfonyl chloride and DMAP in CH_2Cl_2.[20]

SCHEME 6[a]



[a] Reagents and conditions: (a) Ac_2O, DMAP, py (96%); (b) SeO_2, *t*-BuOOH, CH_2Cl_2 (69% at 79% conversion); (c) MsCl, Et_3N, THF, −78 to 0 °C (67% at 84% conversion).

SCHEME 7[a]



[a] Reagents and conditions: (a) *n*-Bu_4NOAc, acetone, reflux (92%); (b) *p*-TsOH, THF, MeOH (83%); (c) $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2, −78 °C (97%); (d) Ph_3PCH_3Br, n-BuLi, THF, −78 to 0 °C (39%); (e) RCM conditions.

The desired mesylation was followed by spontaneous attack of chloride ion at the alternative allyl terminus (see **37**) with concurrent repositioning of the double bond to the intraannular location. This eventuality made possible the acquisition of diacetate **39** by S_N2 displacement with tetrabutylammonium acetate in acetone (Scheme 7).[21] With **39** in hand, it proved an easy matter to effect its conversion to **42** and to explore the susceptibility of this polyolefin to RCM. No linkage between the two terminal double bonds could be accomplished. Complete recovery of starting material following, for example, the heating of **42** with 20 mol % of second-generation Grubbs catalyst in benzene for 16 h was routinely noted. More drastic measures were therefore required.

(17) (a) Marotta, E.; Micheloni, L. M.; Scardovi, N.; Righi, P. *Org. Lett.* **2001**, *3*, 727. (b) For comparison, consult: Kattnig, E.; Albert, M. *Org. Lett.* **2004**, *6*, 945.

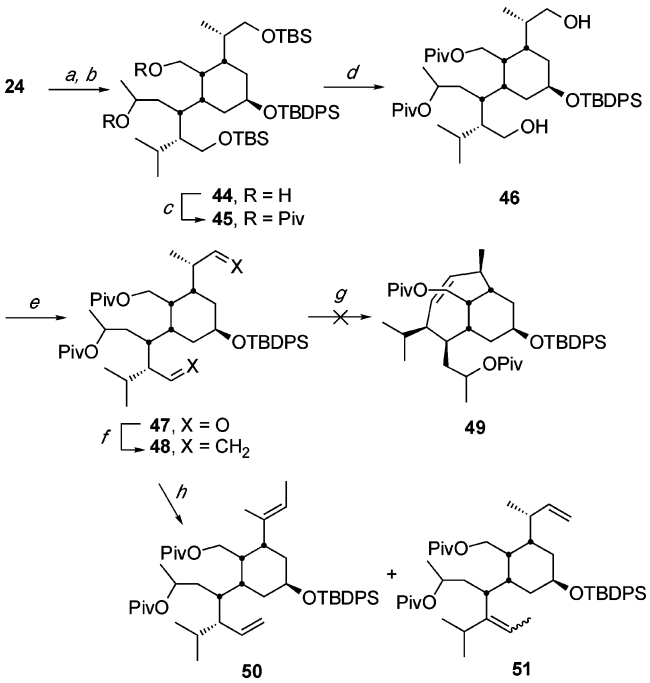
(18) Liu, Z. Unpublished observations.

(19) (a) Umbreit, M. A.; Sharpless, K. B. *J. Am. Chem. Soc.* **1977**, *99*, 5526. (b) Barrero, A. F.; Alvarez-Manzaneda, E.; Altarejos, J.; Salido, S.; Ramos, J. M. *Tetrahedron Lett.* **1994**, *35*, 2945.

(20) Hatakeyama, S.; Numata, H.; Osanai, K.; Takano, S. *J. Org. Chem.* **1989**, *54*, 3515.

(21) Tchilibon, S.; Mechoulam, R. *Org. Lett.* **2000**, *2*, 3301.

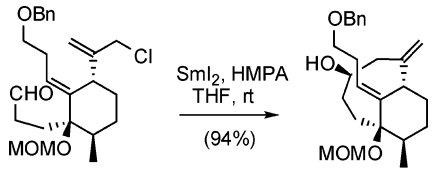
SCHEME 8[a]



[a] Reagents and conditions: (a) O_3, CH_2Cl_2, MeOH, −78 °C then $NaBH_4$, Me_2S, −78 °C, 1 h; (b) $NaBH_4$, EtOH, 0 °C (74% for two steps); (c) PivCl, DMAP, py, rt (89%); (d) *p*-TsOH, THF, MeOH, rt (99%); (e) $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2, −78 °C (91%); (f) Ph_3PCH_3Br, *n*-BuLi, THF, −78 → 0 °C (87%); (g) RCM conditions; (h) Grubbs II catalyst, C_6H_6, Δ (72%).

Reversal in the Timing of Cyclooctene Belt Installation. At this point, the assumption was made that the eight-membered ring might be more amenable to construction if greater degrees of conformational mobility became available. If it is further assumed that this state of affairs would be realized by cleavage of the $\Delta^{3,4}$ π-bond, several candidate precursors are available for consideration. Of these, **24** was selected for investigation. This pragmatic choice was matched with a series of transformations designed to permit regeneration of the cyclohexene ring at the proper time after installation of the belt. This phase of the study began by sequential ozonolysis and reduction with sodium borohydride. As anticipated, diol **44** was efficiently generated (Scheme 8), thereby making possible diesterification with pivaloyl chloride to deliver **45**. Next to be explored was its selective desilylation with *p*-toluenesulfonic acid in a solvent system constituted of THF and methanol. The expectation that **46** would be amenable to conversion to dialdehyde **47** via Swern oxidation was matched by the subsequent Wittig olefination. As encouraging as this sequence was, we were again thwarted by an inability to arrive at **49** via RCM. With either Grubbs catalyst in refluxing CH_2Cl_2, only the recovery of **48** was evidenced. Recourse to higher reaction temperatures (e.g., refluxing benzene) and longer reaction times resulted in partial isomerization to chromatographically inseparable mixtures rich in **50** and **51**.

Overview. In summary, the assembly of enantiopure terminal dienes properly functionalized to serve as possible precursors to vinigrol has been achieved in convergent fashion. The key deterrent to the serviceability of these intermediates (viz., **10**, **22**, **42**, and **48**) is their universal failure to engage in ring-closing metathesis. Our inability to integrate this protocol into rather late stages of the proposed vinigrol synthesis is perceived to arise from steric congestion generated by the numerous side chains that conspire to preclude the necessary proximity of reaction centers. With the structurally less substituted congener **52**, Matsuda has found it possible to arrive at **53** in 98% yield by reduction with samarium iodide under high dilution conditions.[5] The accompanying



52 **53**

two papers describe alternative exploratory efforts to achieve the same objectives by way of a conformational lock model[22] and practical recourse to ring contraction alternatives.[23]

Acknowledgment. Partial financial support was provided by Aventis and the Yamanouchi USA Foundation whom we thank.

Supporting Information Available: Experimental details and high-field ^1H and ^{13}C NMR spectra for all compounds described herein. This material is available free of charge via the Internet at http://pubs.acs.org.

JO048458X

(22) Paquette, L. A.; Efremov, I. *J. Org. Chem.* **2005**, *70*, 510.
(23) Paquette, L. A.; Liu, Z.; Efremov, I. *J. Org. Chem.* **2005**, *70*, 514.