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Exploratory Studies Aimed at a Synthesis of Vinigrol. 4. Probe of Possible Means for Direct Connection of the Side Arms and of Ring-Contraction Alternatives

Leo A. Paquette,* Zuosheng Liu, and Ivan Efremov

Evans Chemical Laboratories, The Ohio State University, Columbus, Ohio 43210

paquette.1@osu.edu

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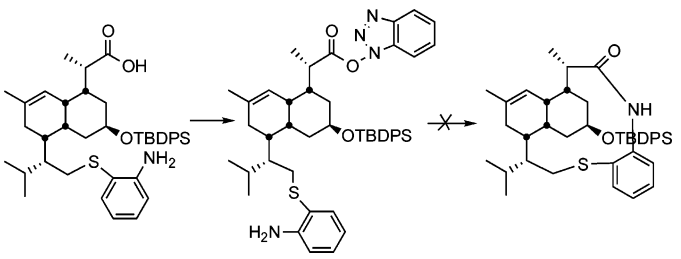

Attempts have been made to gain access to the vinigrol structural framework by way of three routes. These include reductive transannular cyclization, adaptation of the Ramberg−Bäcklund rearrangement, and deployment of the lactam−sulfoxide ring contraction protocol. While the first of these options involves direct transannular C−C bond formation, the other two embody the concept of larger ring construction as a prelude to ring contraction. The initial installation of a sulfur atom involves prior thiacyclononane formation, a process believed to be potentially easier to accomplish. However, arrival at **13**, **14**, or **17** was not achieved. Installation of the heterocyclic ring contained in **31** proved to be equally problematic. Increased disassembly of the molecular structure as featured in dibromide **20** did allow for direct conversion to sulfone **22**. This advanced building block proved not be conducive to in situ α-chlorination and extrusion of the sulfur atom.

The preceding three papers describe efforts that have been expended for the purpose of reaching the vinigrol framework by strategically different pathways.[1−3] Among the approaches that were addressed were those involving the application of ring-closing metathesis, conformational locking, intramolecular S_N2 displacement, and the like. In light of the failure of these tactics, we hoped to solve the synthesis problem by applying other means for the direct connection of the functionalized side chains. Schemes targeting the contraction of purposely configured larger-ring assemblies were also to be scrutinized. Although these attempts were also not successful, the lessons learned in the course of these studies should prove useful in subsequent investigations and are reported herein.

Reductive Transannular Cyclizations. First to be explored was the feasibility of generating a nucleophilic center at one terminus by halogen−metal exchange or oxidative addition so as to induce intramolecular capture by a carboxaldehyde group at the end of the second arm (Scheme 1). Should the reductive coupling be successful, the hydroxyl group so generated could presumably be easily removed to complete construction of the ansa belt. Access to the requisite intermediate **4** was gained from the known alcohol **1**[1] in uneventful fashion. The practicalities associated with the possible conversion of **4** to **5** involved recourse to high dilution conditions, the total absence of moisture, and maintenance of an inert gas atmosphere. First-round screening with Mg, Zn, and Li produced no evidence that **5** had been formed. Under most circumstances, dehalogenated material was isolated as the major component of the reaction mixtures. Unexpectedly, the application of very active metals such as Na and K caused partial degradation of the structural framework (^{1}H NMR). Ultrasonic conditions were probed for their possible positive advantages, but to no avail.

Next to be considered was the option of bringing about the pinacol coupling of dialdehyde **6**[4] (Scheme 2). We were

(1) Paquette, L. A.; Guevel, R.; Sakamoto, S.; Kim, I. H.; Crawford, J. *J. Org. Chem.* **2003**, *68*, 6096.
(2) Paquette, L. A.; Efremov, I.; Liu, Z. *J. Org. Chem*. **2005**, *70*, 505.
(3) Paquette, L. A.; Efremov, I. *J. Org. Chem*. **2005**, *70*, 510.

(4) Crawford, J. Unpublished work from this laboratory.

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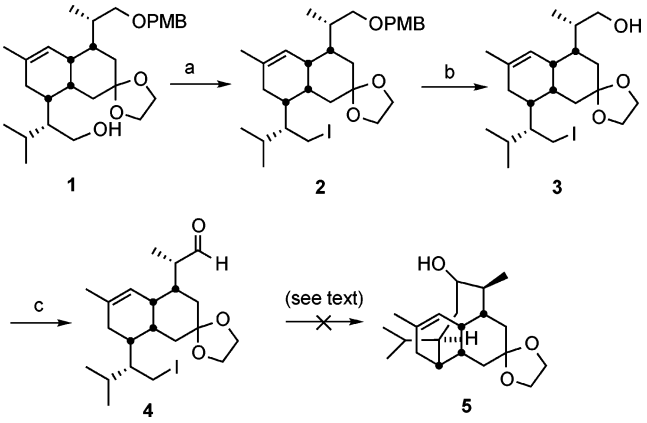
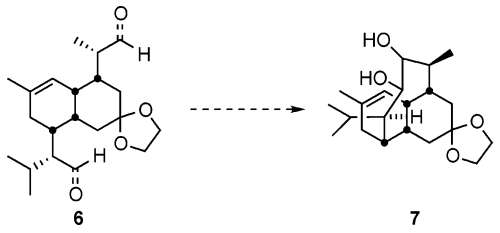
SCHEME 1[a]



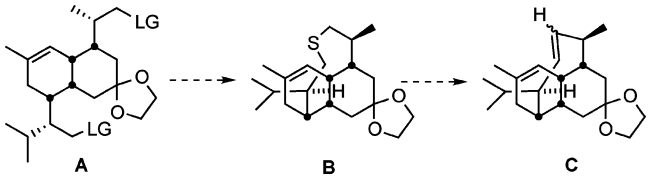
[a] Reagents and conditions: (a) Ph_3P, imidazole, I_2, CH_2Cl_2 (98%); (b) DDQ, CH_2Cl_2, H_2O (99%); (c) Swern oxidation (98%).

SCHEME 2



aware of the possible shortcomings of this protocol from two directions: (a) the unfavorable conformational features of the cis octalin ring system which holds the aldehyde-bearing side chains in a rather distal relationship[1,2] and (b) the fact that a vast majority of pinacol-type reactions are conducted at low temperatures, since they do not require added thermal activation.[5,6] An inability to employ heat as a means of populating alternative, more well-suited conformers of **6** would surely be disadvantageous. These reasons undoubtedly underlie the fact that neither SmI_2 [6d] nor $Zn/TiCl_4$ [6e] induced conversion to **7**.

Strategy Based on Adaptation of the Ramberg−Bäcklund Rearrangement. The formation of a larger cycle followed by ring contraction constitutes an orthogonal route to the vinigrol skeleton. The Ramberg−Bäcklund reaction[7] is exemplary of such applications. In the present context, its adaptation would require initial formation of a thiacyclononane typified by **B**. The prototypical **A** → **B** step can be expected to benefit from the need to generate a larger ring than heretofore, and also from the heightened nucleophilicity of divalent sulfur during the formation of this tricyclic intermediate. To gauge steric accessibility, the first experimental evaluation was performed on derivatives containing the acetal protecting group. At the experimental level, diiodide **9**



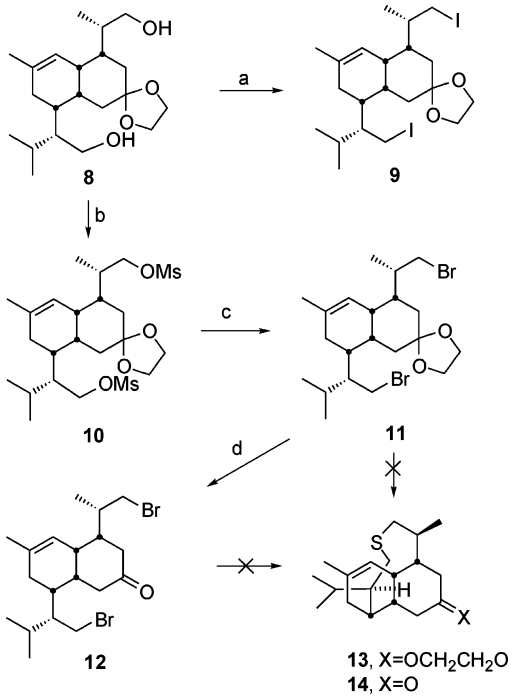
was obtained in a straightforward manner (86% yield) from diol **8**[2] (Scheme 3). When **9** was treated with sodium sulfide under a variety of judiciously chosen conditions consisting mainly of solvent modifications and temperature variations, its proclivity for eliminating HI or underlying only monosubstitution[8] soon became apparent.

We next addressed the acidic hydrolysis of **11** so as to generate dibromo ketone **12** with proportionate reduction in the level of nonbonded steric interactions. Although this transformation was readily accomplished, the recalcitrance of **12** for conversion to **14** paralleled closely that previously observed with **13**. Our recourse to dibromides rather than diiodides was guided by a recent publication[9] that reported a dramatic difference in the behavior of the dihalide alternatives in a similar transformation. It was at this stage that we investigated an analogous reaction with **16**.[8] The question at issue was whether useful levels of cyclization would occur in a precursor having a bulky, equatorially disposed, and therefore conformationally controlling substituent in β-orientation at C(7). Stated differently, would such structural modification facilitate the conformational change conducive to the cyclization reaction? Once again, the outcome was not at all favorable; no spectroscopic indication could be secured that any **17** had been formed (Scheme 4).

Following scrutiny of the above failed transformations, we were of the opinion that success might be realized if enhanced conformational freedom were available. Might the thiacyclononane ring be more readily formed if the cyclohexene ring were first cleaved? Diol **18** was available from an earlier phase of this investigation,[2] and this disassembled structure evolved to serve as our point of departure (Scheme 5). Following conversion to dimesylate **19** in quantitative yield, heating with excess lithium dibromide in refluxing acetone gave dibromide **20** (98%). This intermediate was, inter alia, heated in anhydrous ethanol with a stoichiometric amount of sodium sulfide nonhydrate (1.5×10^{-4} M) under N_2 for 1 day.[9] Only starting material was returned (97% recovery). Alternative recourse to freshly distilled dry HMPA and Na_2S (1.5 equiv)[10,11] for 20 h at 60 °C did not change the outcome. On the other hand, multiple products (but no **21**) were generated when the temperature was increased to 100 °C and reaction time was prolonged to 2 days. Matters took a favorable turn when recourse was made to DMF as the reaction medium. Heating dilute solutions in the 80−95 °C range for a total of 11 h gave rise rather unexpectedly to sulfone **22** in yields ranging from 39 to 72%. We know of no precedent for concurrent oxidation

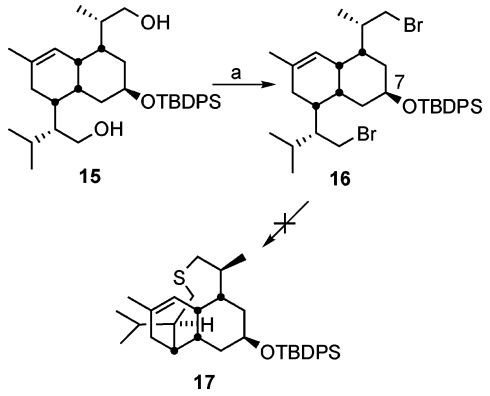
(5) Robertson, G. M. In *Comprehensive Organic Synthesis*; Trost, B. M., Ed.; Pergamon Press: Oxford, 1991; pp 563−610.
(6) (a) Mukaiyama, T.; Sato, T.; Hanna, J. *Chem. Lett.* **1973**, 1041. (b) Corey, E. J.; Danheiser, R. L.; Chandrasekaran, S. *J. Org. Chem.* **1976**, *41*, 260. (c) Imamoto, T.; Kusumoto, T.; Hatanaka, Y.; Yokayama, M. *Tetrahedron Lett.* **1982**, *23*, 1353. (d) Namy, J. L.; Souppe, J.; Kagan, H. B. *Tetrahedron Lett.* **1983**, *24*, 765. (e) McMurry, J. E.; Rico, J. G. *Tetrahedron Lett.* **1989**, *30*, 1169.
(7) (a) Paquette, L. A. *Org. React. (N.Y.)* **1977**, *25*, 1. (b) Taylor, R. J. K.; Casy, G. *Org. React. (N.Y.)* **2003**, *62*, 357.
(8) Efremov, I. V. Ph.D. Dissertation, The Ohio State University, 2001.
(9) MaGee, D. I.; Beck, E. J. *Can. J. Chem.* **2000**, *78*, 1060.
(10) Paquette, L. A.; Wingard, R. E., Jr.; Philips, J. C.; Thompson, G. L.; Read, L. K.; Clardy, J. *J. Am. Chem. Soc.* **1971**, *93*, 4508.
(11) Alvarez, E.; Diaz, M. T.; Liu, H.; Martin, J. D. *J. Am. Chem. Soc.* **1995**, *117*, 1437.

SCHEME 3[a]



[a] Reagents and conditions: (a) Ph_3P, imidazole, I_2, CH_2Cl_2 (86%); (b) MsCl, Et_3N, CH_2Cl_2 (95%); (c) LiBr, acetone, reflux (81%); (d) 1.0 M HCl, acetone (94%).

SCHEME 4[a]

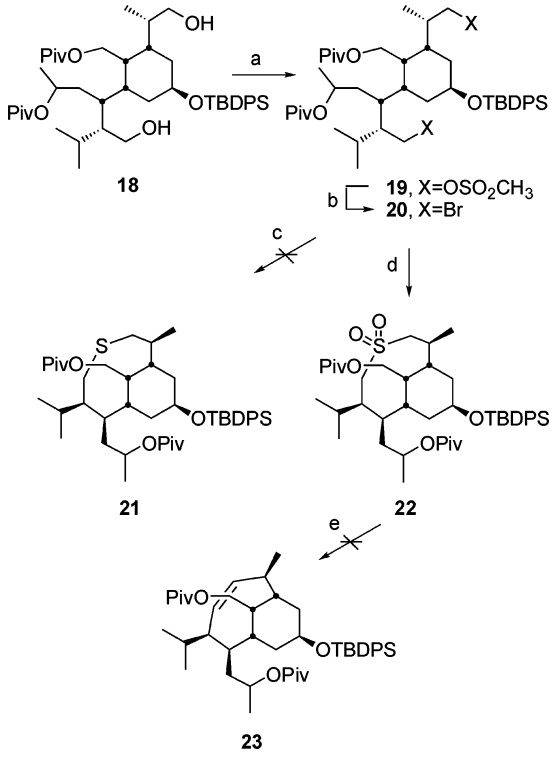


[a] Reagents and conditions: (a) Br_2, Ph_3P, imidazole, CH_2Cl_2; $PhSSO_2Ph$ (57%).

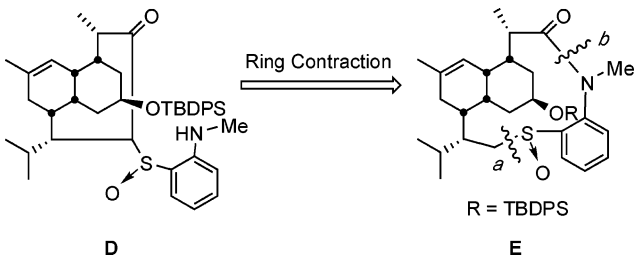
in S_N2 displacements of this type.[12] Our excitement was short-lived, however, when **22** proved unreactive to the action of powdered KOH in a solvent system constituted of CCl_4 and *tert*-butyl alcohol at 50−80 °C for 2 days.[13]

Investigation of the Lactam−Sulfoxide Ring Contraction. In 1983, Ohtsuka and Oishi published their initial report dealing with the synthesis of large-ring lactam sulfoxides and the capacity of these heterocyclic systems to undergo base-promoted cyclization with the extrusion of four atoms.[14] This novel process was subsequently applied by them in tandem with ultimate reductive desulfurization to the successful synthesis of caryophyllenes[15] and taxane diterpenes.[16] The insight gathered from these studies guided our thinking as to the possible implementation of the conversion of **E** to **D** as a means for producing the vinigrol framework. The generation of **E** would entail the requisite formation of a 12-membered ring. Moreover, two different macrocyclic bond assemblies, labeled as *a* and *b* in **E**, suggested themselves as tactical alternatives.

SCHEME 5[a]



[a] Reagents and conditions: (a) MsCl, Et_3N, CH_2Cl_2, 0 °C (100%); (b) LiBr, acetone, reflux (98%); (c) $Na_2S{\cdot}9H_2O$, HMPA, 60 or 100 °C; (d) $Na_2S{\cdot}9H_2O$, DMF, 80−95 °C (39−72%); (e) KOH, CCl_4, *t*-BuOH.



Our first attempt in this connection utilized the previously described **24**[1] as the starting point (Scheme 6). In line with expectation, its OTBS group could be chemoselectively cleaved to give alcohol **25**, the mesylation of which proceeded in 96% yield. Recourse to DDQ in moist

(12) For a discussion of distinctive spectral differences between sulfides and sulfones, see: Tan, L. C.; Pagni, R. M.; Kabalka, G. W.; Hillmyer, M.; Woosley, J. *Tetrahedron Lett.* **1992**, *33*, 7709.

(13) Meyers, C. Y.; Malte, A. M.; Matthews, W. S. *J. Am. Chem. Soc.* **1969**, *91*, 7510.

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(15) Ohtsuka, Y.; Niitsuma, S.; Tadokoro, H.; Hayashi, T.; Oishi, T. *J. Org. Chem.* **1984**, *49*, 2326.

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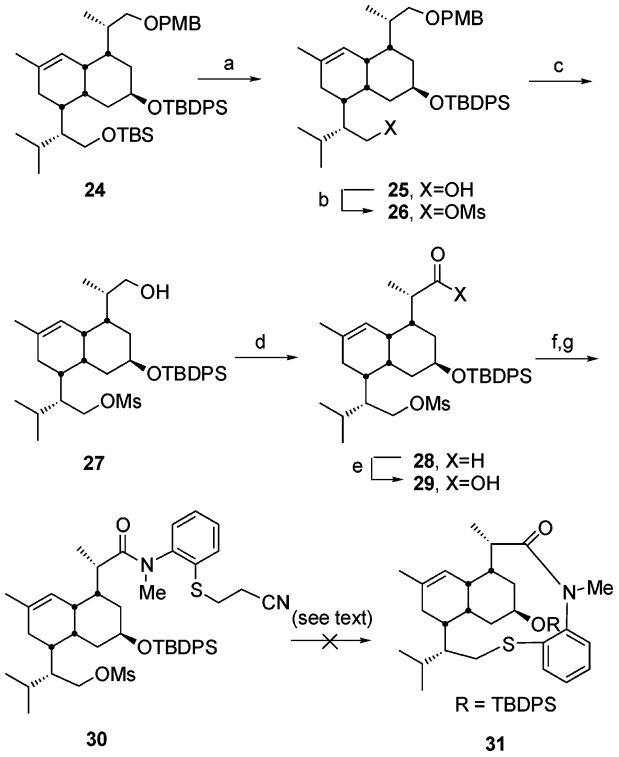
SCHEME 6[a]



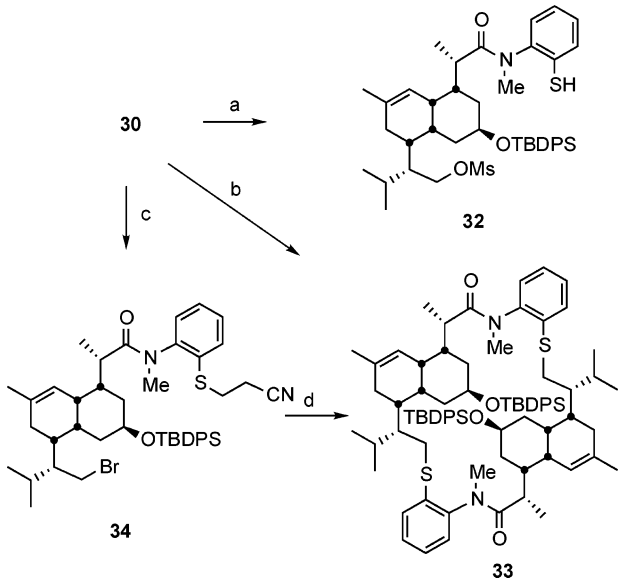
[a] Reagents and conditions: (a) *p*-TsOH, MeOH, THF (100%); (b) MsCl, Et_3N, CH_2Cl_2 (96%); (c) DDQ, CH_2Cl_2, H_2O, rt (95%); (d) $COCl)_2$, DMSO, Et_3N, CH_2Cl_2, −78 °C (91%); (e) $NaClO_2$, NaH_2PO_4, CH_3CN, 2-methyl-2-butene, *t*-BuOH, H_2O (99%); (f) $(COCl)_2$, benzene; (g) *o*-$(MeNN)C_6H_4SCH_2CH_2CN$, K_2CO_3, THF (52% at 57% conversion).

dichloromethane delivered **26** without incurring various undesired side reactions. This alcohol proved useful in that it lent itself to Swern oxidation followed by carboxylic acid generation with sodium chlorite.[17] As events unfolded, the acid chloride derived from **29** was found to have the right combination of overall stability and chemical reactivity to undergo coupling with 2-cyanoethyl 2-(methylamino)phenyl sulfide in very respectable yield (52% at 57% conversion). With **30** in hand, various conditions for effecting cyclization were scrutinized. All involved projected base-promoted elimination to unmask the nucleophilic thiophenoxide anion whose role it was to displace the mesylate group intramolecularly. These steps involved K_2CO_3/$NaBH_4$/DMF/130 °C,[16a] K_2CO_3/$NaBH_4$/DMA/$HOCH_2CH_2OH$/130 °C,[16b] and KO*t*-Bu/*t*-BuOH/dioxane/60 °C.[15] No adjustment of these conditions resulted in other than decomposition of the starting material. No trace of **31** was detected.

At this point, we focused on developing a route to the thiophenol in order to scrutinize its propensity for direct ring closure. The first step, the generation of **32**, was realized by several methods (Scheme 7) with a maximum yield of 64%. This amide was subsequently heated at 66 °C under N_2 and high-dilution conditions (5×10^{-4} M) with THF/HMPA (4:1) as solvent for 3 h. These and related conditions gave rise to the dimer **33** in 30% yield together with 15% of **32**. The option of proceeding forward

(17) Hase, T.; Wähälä, K. In *Encyclopedia of Reagents for Organic Synthesis*; Paquette, L. A., Ed.; Wiley-Chichester, 1995; Vol. 7, p 4533.

SCHEME 7[a]



[a] Reagents and conditions: (a) TBAF, 4 Å MS, THF, reflux; or NaOEt, EtOH, Δ; or NaH, *i*-PrOH, dioxane, reflux (64%); (b) NaH, THF, HMPA, reflux (30%); (c) LiBr, acetone, reflux (88%); (d) NaH, THF, HMPA, reflux (15%).

via bromo amide **34** was also probed. In this case, dimer **33** was produced somewhat less efficiently (15%), and no **34** was recovered.

Our next goal involved more advanced functionalization of the lower side chain in order to install bond *b* last (see **E**). To accomplish this economically, bromo acid **29** was heated to 50 °C with *o*-nitrothiophenol and sodium hydride in a solvent system composed of THF and DMF (Scheme 8). Compound **35** was formed in 97% yield. Reduction of **35** with zinc dust and ammonium chloride in methanol delivered amino acid **36** with reproducible high efficiency.

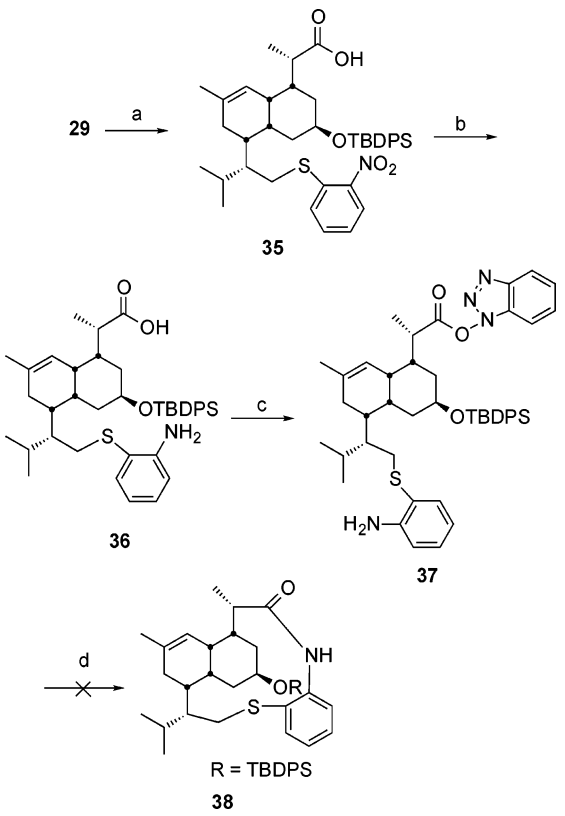
At last, we had brought the synthetic plan to near fruition, in that **36** represented a substance enjoying close correspondence to **E**. However, when we turned to the amide-forming cyclization, it too proved to be very demanding. Reaction with HBTU (4 equiv)[18] and diisopropylethylamine (10 equiv) in DMF did not lead as hoped to the observable formation of **38**. Rather, in its stead, there resulted the benzotriazole-activated ester **37** in 40% yield. Heating a solution of **37** in toluene containing diisopropylethylamine[19] likewise did not provide macrocycle **38**. Consequently, we were unable to examine the feasibility of the Ohtsuka−Oishi ring contraction in this particular context.

Overview. In summary, our exploration of several routes for elaborating the tricyclic ring system of vinigrol has not resulted in formation of the ansa bridge, even when the side chains were extended to make allowance for later ring contraction. Insights gained from an early crystal structure[1] implicate inadequate conformational flexibility of the octalin core despite the cis-fused nature of the rings. Matters do not seem to be materially

(18) Taylor, R. E.; Chen, Y.; Beatty, A.; Myles, D. C.; Zhou, Y. *J. Am. Chem. Soc.* **2003**, *125*, 26.

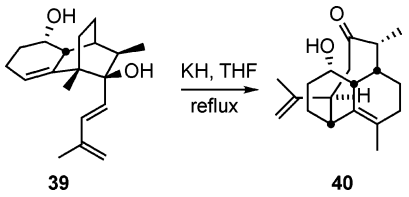
(19) Hatakeyama, S.; Numata, H.; Osanai, K.; Takano, S. *J. Org. Chem.* **1984**, *54*, 3515.

SCHEME 8[a]



[a] Reagents and conditions: (a) *o*-$O_2NC_6H_4SH$, NaH, THF, DMF, 50 °C (97%); (b) An, NH_4Cl, MeOH (90%); (c) HBTU, $(i\text{-Pr})_2NEt$, DMF (41%); (d) $(i\text{-Pr})_2NEt$, toluene, reflux.

different when prior cleavage of one of the constituent rings is performed additionally as in dibromide **20**. It appears that mutual approach of the functionalized centers is strictly avoided. To the extent that this assumption is correct, the central task of closing the third ring may well be accomplished at an earlier stage. One approach to the problem from this direction has been reported by Hanna and co-workers.[20] The Palaiseau group exploited the anionic oxy-Cope rearrangement as the means for transforming **39** into **40**. Although this structural reorganization is subject to wide differences in reactivity and to alternative fragmentation processes, it does offer the attractive capability of rapidly delivering functionalized octahydro-1,5-butanonaphthalenes stereoselectively and concisely.



By extension, routes to a broad selection of enantiopure bicyclic cis-fused octalins have been developed during the present extended investigation. From such compounds might well arise a fuller definition of the structural requirements conducive to the uneventful fabrication of this intriguing class of compounds.

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.

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(20) (a) Devaux, J.-F.; Hanna, I.; Lallemand, J.-Y. *J. Org. Chem.* **1997**, *62*, 5062. (b) Gentric, L.; Hanna, I.; Ricard, L. *Org. Lett.* **2003**, *5*, 1139. (c) Gentric, L.; Hanna, I.; Huboux, A.; Zaghdoudi, R. *Org. Lett.* **2003**, *5*, 3631.