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Exploratory Studies Aimed at a Synthesis of Vinigrol. 3. Evaluation of a Lactone Bridge as a Conformational Lock

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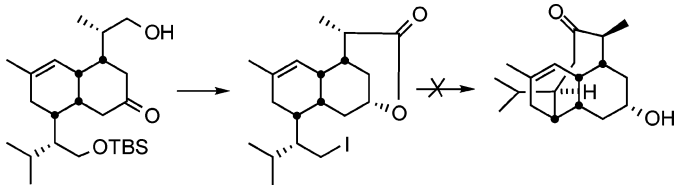
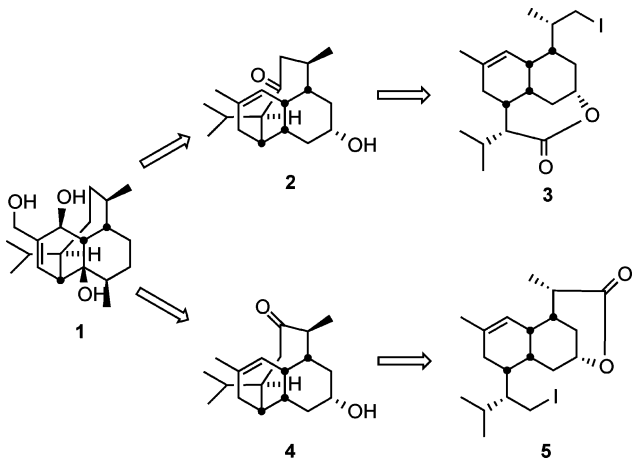


Evaluated in the present investigation are possible synthetic approaches to vinigrol based on the involvement of lactone rings as tools for the conformational rigidification of functionalized *cis*-octalins. Emphasis was placed on the structural arrangements resident in **3** and **5**. The first of these systems proved to be highly strained and inaccessible. Especially notable was the finding that hydroxy ketenes **14** and **21** could be isolated and shown not to be amenable to cyclization when heated. The stereocontrolled assembly of **5** was successfully accomplished through exploitation of a related synthetic pathway. However, neither this attractive intermediate nor its close relative **33** could be processed in a manner that delivered the vinigrol framework. Nonetheless, several features of the routes deployed offer the prospect of wider application in other contexts.

Since our attempts to advance syntheses of vinigrol (**1**) either by intramolecular S_N2 chemistry[1] or by ring-closure metathesis[2] were not rewarded with success, the deliberate decision was made to alter the system significantly by imposing a suitable form of structural constraint. Iodolactones **3** and **5** came to be regarded as candidates suited to our objectives. The projected use of **3** and **5** is reminiscent of a strategy employed by Woodward in his reserpine synthesis.[3]

The perceived practical advantages of this approach included the possible operation of stepwise conformational change and the availability of a large array of lactonization protocols. In addition, the transformations **3** → **2** and **5** → **4** are to be driven by the migration of negative charge from carbon (where it is generated by metal−halogen exchange or oxidative addition) to oxygen, a process that provides a thermodynamic driving force for the reactions under consideration.

The plan of action was supported by molecular mechanics calculations[4] involving **3** and **5**. Two rather dissimilar conformations prevail in each instance. The differences in energy between the conformations are compiled in Table 1. Of special note was the determination that **3a** and **5b** are virtually isoenergetic. This consideration gave rise to the assumption that interconversion between the two conformers might well occur freely, thereby allowing for bond-forming processes selected for passage from **3** to **2** to operate without serious impediment.



Since iodolactone **3** offered the greatest promise on the basis of this analysis, a synthetic route to this intermediate was developed first. As outlined in Scheme 1, the

(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) Woodward, R. B.; Bader, F. E.; Bickel, H.; Frey, A. J.; Kierstead, R. W. *Tetrahedron* **1958**, *2*, 1.
(4) Allinger, N. L. *J. Am. Chem. Soc.* **1977**, *99*, 8127.

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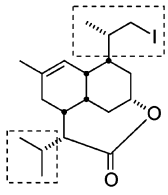
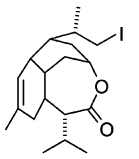
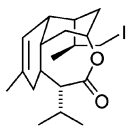
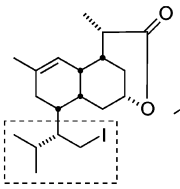
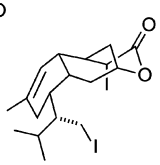
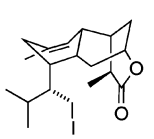
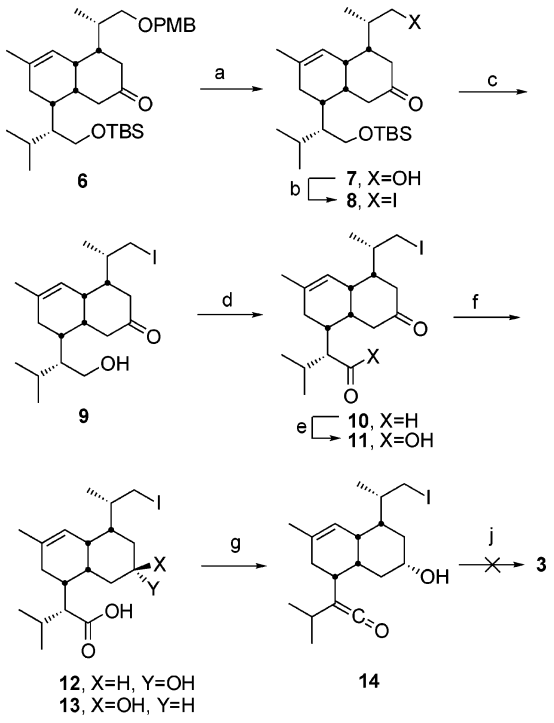
TABLE 1. Calculated Steric Energies for 3 and 5

Iodolactone[a]	More stable equatorial conformer	Less stable axial conformer	ΔE_{steric}, kcal/mol
				0.2
	3	**3a**	**3b**	
				4.7
	5	**5a**	**5b**	

[a] For the calculations, the encased substituents were replaced by methyl groups.

SCHEME 1[a]



[a] Reagents and conditions: (a) DDQ, CH_2Cl_2, H_2O (99%); (b) Ph_3P, imid, I_2, CH_2Cl_2 (94%); (c) 1.0 M HCl, acetone (98%); (c) Dess−Martin periodinane, CH_2Cl_2 (74%); (d) $NaClO_2$, NaH_2PO_4, *t*-BuOH, MeCN, H_2O, 2-methyl-2-butene (quant); $NaBH_4$, EtOH (82% of **12**, 12% of **13**); (g) 2-chloro-1-methylpyridinium iodide, MeCN, reflux, slow addition of **12** and Et_3N (77%); (h) heat in various solvents.

previously described bicyclic ketone **6**[1] was the point of origin. Following the removal of its PMB group by means of DDQ in an aqueous solvent system, the liberated hydroxyl substituent proved amenable to conversion into iodide **8** in 94%yield. The second OH group was liberated under acidic conditions, thereby allowing for conversion to aldehyde **10** by oxidation with the Dess−Martin periodinane reagent.[5] Also encouraging was the uneventful generation of carboxylic acid **11** upon subsequent treatment with buffered sodium chlorite.[6] When **11** was subjected to the action of sodium borohydride, a mixture of α- and *β*-alcohols was produced in 82% and 12% yield, respectively. As a consequence of chromatographic inseparability at this stage, all lactonization protocols were performed on this mixture.

Recourse was initially made to the Corey method,[7] to conditions developed by Yamaguchi,[8] and to reagents such as *p*-toluenesulfonic acid, EDC, and dibutyltin oxide[9] in addition to simple fusion. All such conditions were to no avail, showing no tendency for product formation. In contrast, application of the Mukaiyama cyclization[10] led to clean formation of a single product. The spectral features of this substance, most notably its distinctive infrared (2091, vs), mass spectral (*m/z* 416.1145), and NMR features (δ C=C=O = 204.4, 135.9), confirmed it to be the hydroxy ketene **14**. The stability of this entity is noteworthy. Not only does **14** survive aqueous workup and mildly acidic conditions, but it also can be recovered efficiently from chromatography on silica gel. At this point, thermal cyclization appeared to be an attractive option for the generation of lactone **3**. Based on this line of reasoning, several experiments were undertaken to effect this attractive conversion. However, under no circumstances was cyclized material produced at a useful level. To illustrate, heating dilute, dry solutions of **14** in xylenes (reflux) or 1,2-dimethoxyethane (150 °C, sealed vessel) only returned starting material. A somewhat more gratifying result was realized upon heating in diphenyl ether in that a very small amount of nonpolar material with the correct molecular mass could be recovered. This matter was not further pursued because it obviously lacked preparative utility.

To substantiate our conclusion that the inability of **14** to experience cyclization resides in the elevated ring strain of the lactone, an alternative pathway was pursued wherein the iodine atom would be installed at a post-lactonization stage. This goal was realized by an inversion in the synthetic sequence (Scheme 2). The expectation that **15**[1] could be chemically transformed into hydroxy acid **19** was realized in four efficient steps. Submission of **19** to the Mukaiyama conditions gave rise before to a ketene. Although **21** exhibited no tendency to experience cyclization to form lactone **22** under a variety of conditions, this intermediate proved to be quite unstable to acidic conditions and consequently did not lend itself to further modification.

The preceding observations were meaningful in contributing to our improved understanding of the three-dimensional properties of these all-cis octalin systems. The formation of lactones **3** and **22** is dependent on the operation of conformational changes in both six-membered rings. Were this state of affairs readily attainable, elaboration of the vinigrol framework would presumably

(5) Dess, D. B.; Martin, J. C. *J. Org. Chem.* **1983**, *48*, 4155.
(6) Hase, T.; Wähälä, K. In *Encyclopedia of Reagents for Organic Synthesis*; Paquette, L. A., Ed.; Wiley: Chichester, 1995; Vol. 7, p 4533.
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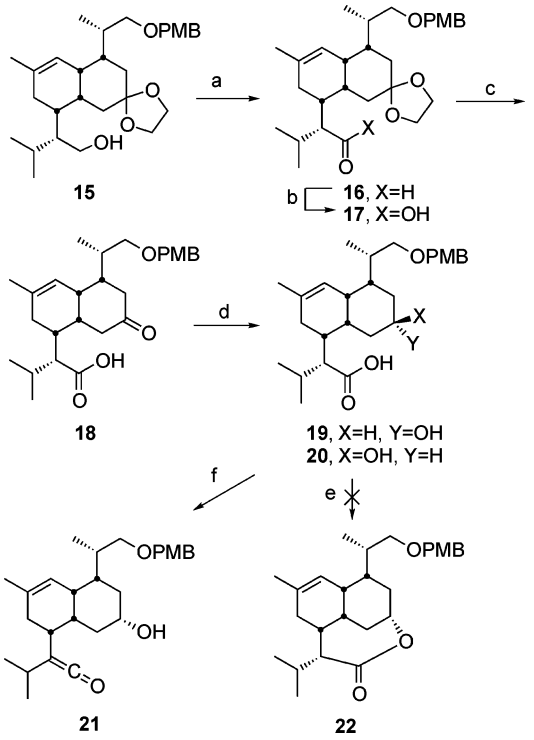
(8) Inanaga, J.; Hirata, K.; Saeki, H.; Katsuki, T.; Yamaguchi, M. *Bull. Chem. Soc. Jpn.* **1979**, *52*, 1989.
(9) Steliou, K.; Szczygielska-Nowosielska, A.; Favre, A.; Poupart, M. A.; Hanessian, S. *J. Am. Chem. Soc.* **1980**, *102*, 7578.
(10) Mukaiyama, T.; Usui, M.; Saigo, K. *Chem. Lett.* **1976**, 49.

SCHEME 2[a]



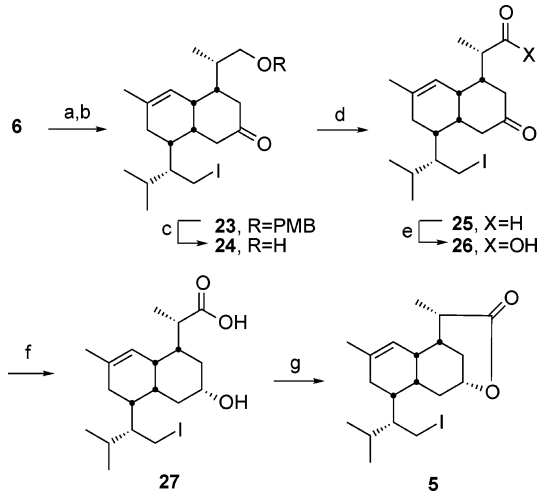
[a] Reagents and conditions: (a) Swern oxidation (86%); (b) $NaClO_2$, NaH_2PO_4, *t*-BuOH, MeCN, H_2O, 2-methyl-2-butene (quant); (c) 1.0 M HCl, acetone; (d) $NaBH_4$, EtOH (89%, two steps); (e) from **19**, Ph_3P, DEAD, THF, 0 °C; (f) 2-chloro-1-methylpyridinium iodide, MeCN, reflux with slow addition of **20** and Et_3N (73%).

ensue with relative ease. Our findings suggest this route not to be viable. We undertook therefore to pursue the construction of lactone **5**. This intermediate could prove to be a viable alternative since the cyclization leading to this entity requires conformational flexing only within a single ring. Should sufficient energy then be provided to invert the second ring, the reactive functionalities would be brought into proximity with each other and a second cyclization leading to the vinigrol framework could operate.

Ultimately, a set of conditions was devised to provide **5** (Scheme 3). With ketone **6** as the point of departure, the "lower" hydroxyl group was chemoselectively unmasked and converted to the iodo derivative **23**. There followed oxidative cleavage of the PMB group to give **24**, thereby setting the stage for two-step oxidation to carboxylic acid **26**. Treatment of **26** with sodium borohydride led predominantly to **27**, which underwent conversion to lactone **5** upon application of the Mukaiyama conditions. The yield of 44% is not considered to be optimized.

With **5** in hand, the time had come to explore intramolecular opening of its lactone ring. In a first experiment, *tert*-butyllithium was added in an attempt to bring about halogen−metal exchange, with nucleophilic attack at the lactone carbonyl expected to follow.[11] No cyclization occurred at low temperatures. When heat was applied incrementally, several products were obtained, each of which had an intact lactone ring. On the strength of

SCHEME 3[a]



[a] Reagents and conditions: (a) 1.0 M HCl, acetone (quant); (b) Ph_3P, imid, I_2, CH_2Cl_2 (91%); (c) DDQ, CH_2Cl_2, H_2O (quant); (d) Swern oxidation (96%); (e) $NaClO_2$, NaH_2PO_4, *t*-BuOH, MeCN, H_2O, 2-methyl-2-butene (quant); (f) $NaBH_4$, EtOH (84%); (g) 2-chloro-1-methylpyridinium iodide, MeCN, reflux; slow addition of **27** and Et_3N (44%).

strong literature precedent,[12] **5** was also treated with zinc powder in DME containing sodium iodide and water. Only deiodinated material was obtained in 67% yield. If water was scrupulously removed from the reaction mixture and heating was applied incrementally, gradual decomposition was uniquely observed. Barbier-type reactions featuring magnesium as the active metal were likewise examined, but without success. Various modifications of Molander's protocol[13] also met with disappointment.

For these reasons, we were directed to the examination of other less obvious synthetic options. A ploy considered interesting involved the possible conversion of aldehyde **33** to its dithioacetal **34** in preparation for the possible olefination involving the lactone carbonyl. Titanium-promoted reactions of this type have been developed by Takeda.[14] In this particular instance, treatment of the intermediate enol ether with acid would give rise to the targeted tricyclic structure **35** (Scheme 4). The availability of **33** could allow as well for examination of its response to McMurry reaction conditions.[15] Although the intermediate enol ether would be rather strained, the possibility exists that the chelating effect of titanium might prove to serve as a significant driving force for C−C bond formation.

The preparation of lactone aldehyde **33** began with the previously accessed **7**. Oxidation of its primary hydroxyl to the carboxylic acid level was performed as before. The conversion of **29** to **30** made possible arrival at lactone **31** (49%). Unexpectedly, this material proved to be an unusually unstable compound. An underlying reason for this phenomenon may be the presence of a space-demanding −OTBS group in the interior of the molecule,

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(12) Astudillo, L.; González, A. G.; Galindo, A.; Mansilla, H. *Tetrahedron Lett.* **1997**, *38*, 6737.

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(14) Rahim, M. A.; Sasaki, H.; Saito, J.; Fujiwara, T.; Takeda, T. *J. Chem. Soc., Chem. Commun.* **2001**, 625.

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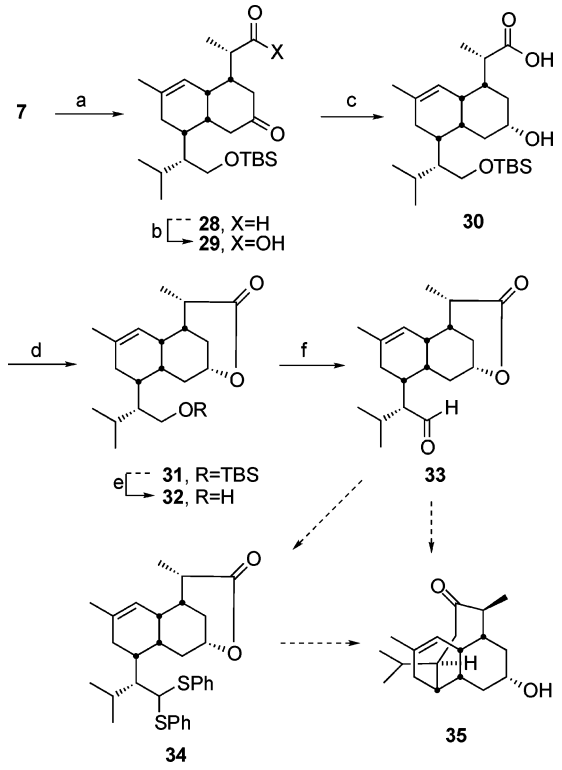
SCHEME 4[a]



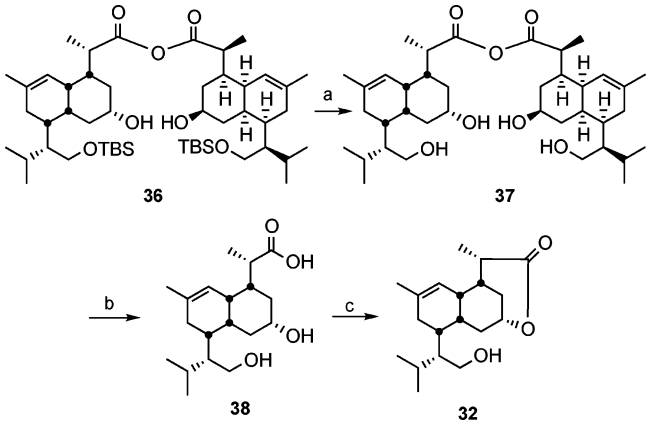
[a] Reagents and conditions: (a) Swern oxidation (95%); (b) $NaClO_2$, NaH_2PO_4, *t*-BuOH, MeCN, H_2O, 2-methyl-2-butene (quant); (c) $NaBH_4$, EtOH (91%); (d) 2-chloro-1-methylpyridinium iodide, MeCN, reflux; slow addition of **30** and Et_3N (49%); (e) HF–pyridine, THF (89%); (f) Dess–Martin periodinane, CH_2Cl_2 (91%).

which translates into a rapid rate of hydrolysis of the lactone bridge. While removal of the silyl protecting group in **31** was consequently not a trivial task, it ultimately proved possible to obtain **32** and to implement its oxidation to **33** by means of the Dess–Martin periodinane reagent.

A major byproduct of the lactonization step was anhydride **36**, isolated in 35% yield (Scheme 5). This compound is the obvious end result of the intermolecular capture of an activated form of the carboxylic acid, perhaps the ketene, with a second molecule of **30**. Compound **36** becomes **37** on desilylation, thereby enabling recycling to **32** via **38**. The recalcitrance of the anhydride linkage in **36** and **37** to hydrolysis is noteworthy. For the conversion of **37** to **38** to proceed at a reasonable rate, it was necessary to use 30% HCl in THF. Advancement via Scheme 5 appeared to offer no advantages relative to the forward progress defined in Scheme 4.

The time had arrived to investigate the possibility of converting **33** into **35** by means of the McMurry reaction. Although keto-ester couplings have been successfully performed with ketones only,[16] the higher reactivity of aldehydes could make matters problematic. $TiCl_3/LiAlH_4$ is recognized to be superior to the $TiCl_3$/Zn–Cu-based

SCHEME 5[a]



[a] Reagents and conditions: (a) 1.0 M HCl, THF (22%); (b) concd HCl, THF (85%); (c) 2-chloro-1-methylpyridinium iodide, MeCN, reflux; slow addition of **38** and Et_3N (38%).

method,[15,16] and the latter conditions were therefore utilized. Unfortunately, extensive decomposition occurred and none of the desired product was detected. When the second important observation was made that **33** could not be transformed into dithioacetal **34** in the presence of Lewis acids,[17] further studies along these lines were shelved in favor of alternative ring contraction approaches.[18]

Overview. The use of a lactone bridge as a device to merge otherwise awkwardly positioned functional side chains has been explored. In the first instance involving the structural elements resident in **3**, high levels of ring strain precluded assembly of the lactone ring. This state of affairs became most clearly apparent when hydroxy ketenes **14** and **21** failed to cyclize when thermally activated. Lactone intermediates of type **5** did prove amenable to synthesis as reflected in the production of **31**–**33** as well. Although this collective group of compounds exhibited a reasonable level of hydrolytic stability, their potential for added intramolecular C–C bond formation could not be reduced to practice. The variety of reductive ways deployed to achieve a desirable coupling result validates the difficulties associated with generation of the vinigrol framework.

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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