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Iodine(III)-Promoted Ring Expansion of 1-Vinylcycloalkanol Derivatives: A Metal-Free Approach toward Seven-Membered Rings†

Luiz F. Silva, Jr.,* Ramon S. Vasconcelos, and Mário A. Nogueira

Instituto de Química, Universidade de São Paulo, Avenida Professor Lineu Prestes, 748, CP 26077, CEP 05513-970 São Paulo SP, Brazil

luizfsjr@iq.usp.br

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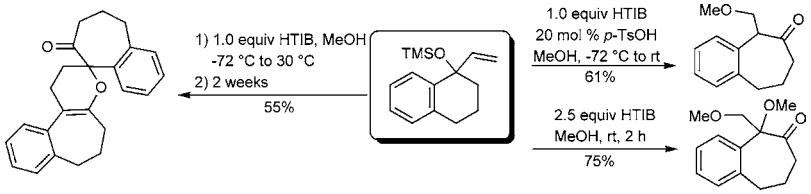
ABSTRACT



A versatile and metal-free approach for the synthesis of molecules bearing seven- and eight-membered rings is described. The strategy is based on the ring expansion of 1-vinylcycloalkanols (or the corresponding silyl or methyl ether) mediated by the hypervalent iodine reagent HTIB (PhI(OH)OTs). The reaction condition can be easily adjusted to give seven-membered rings bearing different functional groups. A route to medium-ring lactones was also developed.

A seven-membered ring fused to an aromatic ring is present in several compounds with remarkable biological activity. Examples are: (a) theaflavin,[1a] which is a promising anticancer compound present in black tea; (b) colchicine,[1b] which has several properties; and (c) TAK-779,[1c] which has anti-HIV-1 activity (Figure 1). Thus, the research in this area has been very active.[1−2] Whereas uncountable methodologies are available to obtain five- and six-membered rings, the construction of seven-membered rings is an unsolved problem in synthesis, mainly because in the latter system

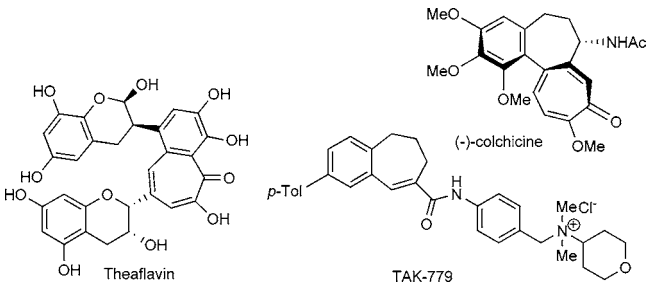


Figure 1. Natural products bearing a seven-membered ring.

cyclization reactions suffer from several limitations.[3] In this scenario, the synthesis of seven-membered ring derivatives remains to be a challenging endeavor in synthetic organic chemistry. An attractive route to obtain a seven-membered

† This paper is dedicated in memory of Prof. Helena Ferraz.

(1) For leading references, see: (a) Yang, C. S.; Lambert, J. D.; Ju, J.; Lu, G.; Sang, S. *Toxicol. Appl. Pharmacol.* **2007**, *224*, 265. (b) Graening, T.; Schmalz, H.-G. *Angew. Chem., Int. Ed.* **2004**, *43*, 3230. (c) Baba, M.; Nishimura, O.; Kanzaki, N.; Okamoto, M.; Sawada, H.; Iizawa, Y.; Shiraishi, M.; Aramaki, Y.; Okonogi, K.; Ogawa, Y.; Meguro, K.; Fujino, M. *Proc. Natl. Acad. Sci. U.S.A.* **1999**, *96*, 5698.

(2) For some examples, see: (a) Majetich, G.; Zou, G. *Org. Lett.* **2008**, *10*, 81. (b) Aïssa, C.; Fürstner, A. *J. Am. Chem. Soc.* **2007**, *129*, 14836. (c) Simmons, E. R.; Yen, J. R.; Sarpong, R. *Org. Lett.* **2007**, *9*, 2705. (d) For a review concerning cycloadditions, see: Battiste, M. A.; Pelphrey, P. M.; Wright, D. L. *Chem.−Eur. J.* **2006**, *12*, 3438. (e) For a review concerning ring expansions, see: Kantorowski, E. J.; Kurth, M. J. *Tetrahedron* **2000**, *56*, 4317.

(3) For selected reviews, see: (a) Molander, G. A. *Acc. Chem. Res.* **1998**, *31*, 603. (b) Illuminati, G.; Mandolini, L. *Acc. Chem. Res.* **1981**, *14*, 95; See also refs 2d−e.

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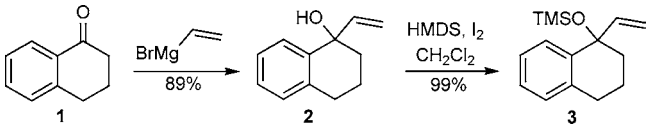
ring is the ring expansion of a readily available six-membered ring substrate.[2e,4] This approach has been applied to prepare ring expanded enones by the rearrangement of protected 1-alkenyl-1-cycloalkanols mediated by Tl(III),[4a] Pd(II),[4b,c] and Hg(II).[4d] Intense efforts are underway to avoid the use of heavy metals in chemistry. In this context, hypervalent iodine compounds constitute a class of reagents that can be used for a number of oxidative transformations with high levels of selectivity.[5] Thus, we decided to study the reactivity of 1-vinylcyclohexanol derivatives toward PhI(OH)OTs (HTIB or Koser's Reagent)[5f] to develop metal-free routes to seven-membered ring derivatives.

An efficient method to prepare the substrates was the first goal of our study. The reaction of 1-tetralone (**1**) with CH_2=CHMgBr gave the unsaturated 1-tetralol **2** in 89% yield.[6] Considering the possible instability of the tertiary benzylic and allylic alcohol **2**, we decided to protect it as the TMS ether. The protocol using TMSCl/HMDS in reflux of hexane was applied to **2**, giving the desired product **3** in only 11% yield. However, we were delighted to find that using HMDS in the presence of a catalytic amount of I_2 gave **3** cleanly in 99% yield (Scheme 1).[7]

Scheme 1. Preparation of the Unsaturated TMS Ether **3**



The above two-step sequence was then applied to several ketones, leading to **4**−**10**. We were also interested in the behavior of alkyl ethers. Thus, the methyl ether **11** was prepared treating **2** with KOH/MeI (Figure 2).[8] We first performed a detailed investigation on the reactivity of the TMS-protected 1-vinylcycloalkanol **3** focusing on HTIB, based on previous works.[9] Thus, treatment of **3** with HTIB in CH_3CN, in trimethylorthoformiate or without solvent,[10] led to a complex mixture of compounds. Fortunately, when the unsaturated TMS-ether **3** was treated with HTIB in MeOH in the presence of *p*-TsOH,[11] TLC analysis indicated the cleavage of the labile TMS-group. Then, the alcohol **2** formed in the medium reacted with iodine(III), giving the ring expansion product **12**, in 61% yield (Table 1, entry 1).

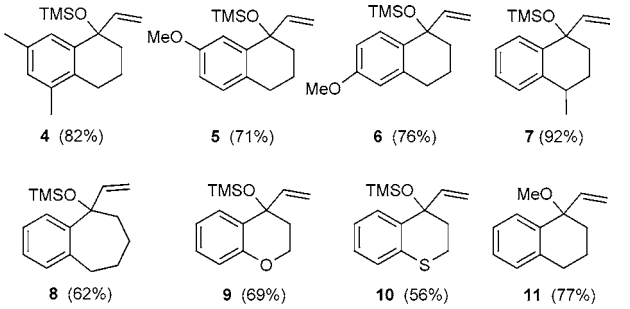


Figure 2. Structures of the substrates **4**−**11**.

Table 1. HTIB-Mediated Ring Expansion of **3**

entry	conditions	product (isolated yield)
1	1.0 equiv HTIB, 20 mol % *p*-TsOH, MeOH, -72 °C to rt, 2 h	**12** (61%)
2	1.0 equiv HTIB, MeOH, -72 to 30 °C, 2.5 h	**13** + **14** 72% (4:1)
3	1) 1.0 equiv HTIB, MeOH, -72 to 30 °C, 2.5 h; 2) 2 weeks	**14** (55%)
4	2.5 equiv HTIB, MeOH, rt, 2 h	**15** (75%)

The methoxy-ketone **12** would be originated from **3** in four steps. The first would be the acid-catalyzed deprotection of the TMS group, giving **2**, on which the electrophilic addition of iodine(III) to the double bond would give the cation **16**. Migration of the aryl carbon would lead to **17**. Finally, a reductive solvolysis on **17** would produce the methoxylated ketone **12**. Higher temperatures and longer reaction times promote an acid-catalyzed elimination of MeOH from **12**, furnishing the enone **13** (Scheme 2), together with the dimer **14** (Table 1, entry 2).[12] This result is slightly different from that using Tl(III), which gives only the enone **13** from **3**.[4a]

On standing, the mixture **13**/**14** gave only **14**, in 55% yield (entry 3), whose structure was determined by X-ray analysis (see Supporting Information). The pentacyclic compound **14**

(4) (a) Kim, S. G.; Uh, K. H. *Tetrahedron Lett.* **1996**, *37*, 3865. (b) Trost, B. M.; Xie, J. *J. Am. Chem. Soc.* **2006**, *128*, 6044. (c) For a review concerning Pd reactions, see: Muzart, J. *Tetrahedron*, **2005**, *61*, 9423. (d) Kim, S.; Uh, K. H. *Tetrahedron Lett.* **1992**, *33*, 4325. (e) Kim, S.; Park, J. K. *Tetrahedron Lett.* **1989**, *30*, 6181.

(5) For some reviews concerning hypervalent iodine, see: (a) Ochiai, M. *Chem. Rec.* **2007**, *7*, 12. (b) Richardson, R. D.; Wirth, T. *Angew. Chem., Int. Ed.* **2006**, *45*, 4402. (c) Ladziata, U.; Zhdankin, V. V. *Arkivoc* **2006**, *9*, 26. (d) Silva, L. F., Jr. *Molecules* **2006**, *11*, 421. (e) Zhdankin, V. V.; Stang, P. J. *Chem. Rev.* **2002**, *102*, 2523. (f) For a review concerning HTIB, see: Koser, G. F. *Aldrichim. Acta* **2001**, *34*, 89.

(6) Schmidt, B. *J. Org. Chem.* **2004**, *69*, 7672.

(7) Karimi, B.; Golshani, B. *J. Org. Chem.* **2000**, *65*, 7228.

(8) Johnstone, R. A. W.; Rose, M. E. *Tetrahedron* **1979**, *35*, 2169.

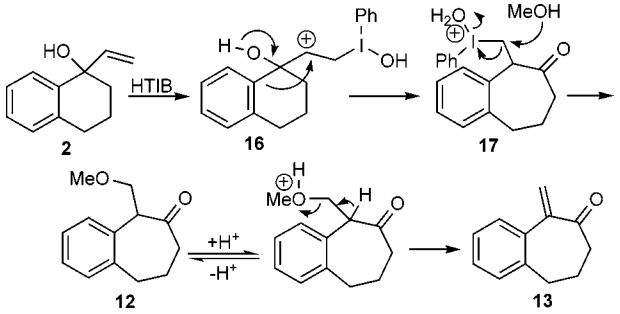
(9) For some papers concerning the use of HTIB in rearrangements, see: (a) Justik, M. W.; Koser, G. F. *Tetrahedron Lett.* **2004**, *45*, 6159. (b) Justik, M. W.; Koser, G. F. *Molecules* **2005**, *10*, 217. (c) Silva, L. F., Jr.; Siqueira, F. A.; Pedrozo, E. C.; Vieira, F. Y. M.; Doriguetto, A. C. *Org. Lett.* **2007**, *9*, 1433. (d) See also ref 5.

(10) Yusubov, M. S.; Wirth, T. *Org. Lett.* **2005**, *7*, 519.

(11) The HTIB-mediated rearrangement of 1-vinylcycloalkanol derivatives, such as **3**, **9**, and **10**, occurs in a cleaner manner in the presence of *p*-TsOH than without it, because the formation of the reactive species $[PhIOH]^+$ is probably an acid-catalyzed auto-catalytic process.

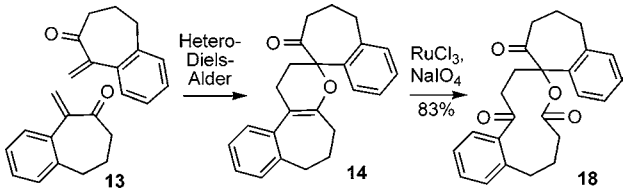
(12) TLC analysis showed that **14** is formed after the work-up.

Scheme 2. Ring Expansion of **2** with 1.0 equiv of HTIB



is formed from the 1-vinylcycloalkanol derivative **3** in a single operation through a tandem ring-expansion/hetero-Diels−Alder reaction. We envisioned that **14** could be used to obtain a medium ring lactone.[13] Indeed, the oxidative cleavage of the double bond of **14** could be performed with $RuCl_3/NaIO_4$, giving the 11-membered ring keto-lactone **18** (Scheme 3). In summary, the commercially available 1-

Scheme 3. Preparation of the Medium-Ring Keto-Lactone **18**

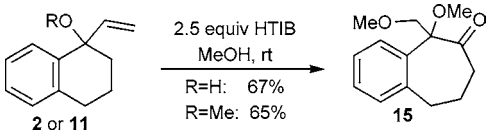


tetralone (**1**) was transformed in only four steps into **18**, which bears a spiro seven-membered ring and a medium-ring lactone. Thus, in this short sequence of steps, the molecular complexity is greatly increased, because several reactions took place in a few operations.

Because the enone **13** is prone to further oxidation, we decided to investigate the reaction of **3** with excess of oxidant. When **3** was treated with 2.5 equiv of HTIB, a tandem ring expansion/addition of MeOH gave the dimethoxy-ketone **15** (entry 4, Table 1). An iodine(III)-mediated electrophilic addition of MeOH to the enone **13** would give **15**. As shown in Table 1, different ring expansion products can be obtained from **3** just by the modification of the reaction conditions.

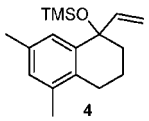
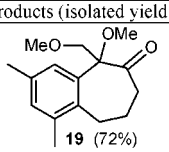
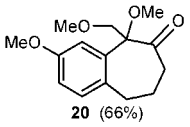
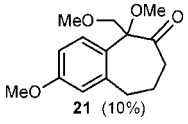
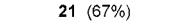
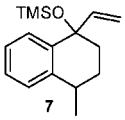
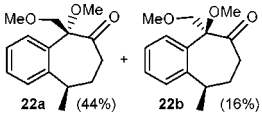
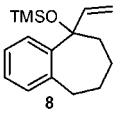
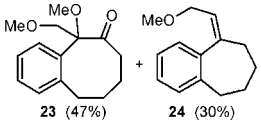
After exploring the oxidation of **3** with iodine(III) under several conditions, other parameters in the reaction were studied. First, we checked if the protection as a silyl ether was really required. The desired dimethoxy-ketone **15** was also obtained when either **2** or **11** were treated with HTIB (Scheme 4). Therefore, the presence of the TMS group is not essential for the ring expansion, although higher yields of the desired product were observed from **3** (75%) than from **2** or from **11** (65−67%).

Scheme 4. Tandem Expansion/Addition of **2** and **11** by HTIB



A group in the aromatic ring could modify the migratory aptitude of the migrating carbon, which may influence the yield of the rearrangement product.[14] The TMS-protected alcohol **4**, which bears methyl groups, gave the dimethoxy ketone **19** (Table 2, entry 1) in a similar yield to the

Table 2. I(III)-Promoted Tandem Ring Expansion/Addition

entry	substrate	products (isolated yield)
1[a]		
2[a]		
3[a]		
4[b]		
5[a]		
6[a]		

[a] MeOH. [b] AcOEt:MeOH: 2:1.

nonsubstituted substrate **3**. A methoxy group at the meta position could decrease the migratory aptitude of the migrating carbon.[15] Hence, a lower yield of the ring expansion product should be expected. However, the reaction of **5** with HTIB also gives the desired product (**20**) in comparable yield (entry 2). On the other hand, the reaction with **6** was sluggish, leading to the ring expansion product **21** in only 10% yield (entry 3). Eventually, we found that treating **6** with HTIB in a mixture of AcOEt/MeOH gave **21** in 67% yield (entry 4). The substrate **7** was exposure to HTIB giving **22a/b** in 44 and 16% yield, respectively (entry 5). This selectivity is determined in the addition of iodine(III) to the enone **I**, which

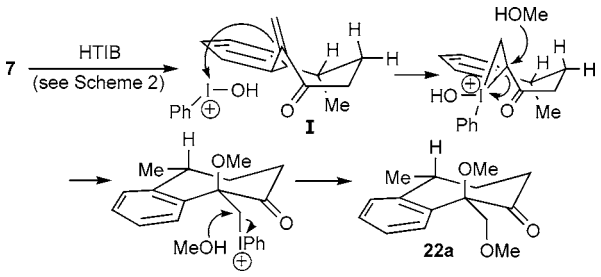
(13) For reviews concerning the synthesis of medium rings lactones, including oxidative cleavage approaches, see: (a) Ferraz, H. M. C.; Bombonato, F. I.; Longo, L. S., Jr. *Synthesis* **2007**, 3261. (b) Rousseau, G. *Tetrahedron* **1995**, *51*, 2777.

(14) A correlation between yield of the product and migratory aptitude was noted in Tl(III)-mediated ring contraction of 1,2-di-hydronaphthalenes: Silva, L. F., Jr.; Sousa, R. M. F.; Ferraz, H. M. C.; Aguilar, A. M. *J. Braz. Chem. Soc.* **2005**, *16*, 1160. See also ref 9c.

(15) The value of the Hammett constant σ_m for OMe is 0.11.

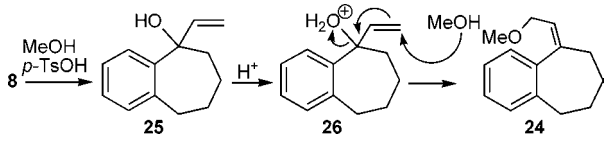
is analogous to **13**. This step would occur preferentially through its less hindered face (Scheme 5). The possibility

Scheme 5. Mechanism for the Formation of **22a**



of using a ring expansion reaction to prepare eight-membered rings was also investigated. The substrate **8** was treated with HTIB, giving the desired eight-membered ring compound **23** and the unsaturated ether **24**[16] (entry 6). Although the yield of the desired product **23** was moderate, this route can be useful to obtain eight-membered ring derivatives, because only three steps are necessary to obtain **23** from the commercially available benzosuberone. The formation of **24** can be explained by an acid-catalyzed S_N2' reaction (Scheme 6).

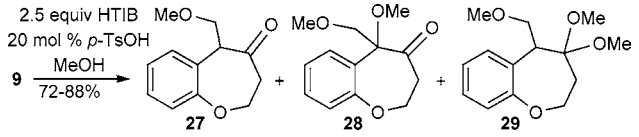
Scheme 6. Acid-Catalyzed S_N2' Reaction of **8**



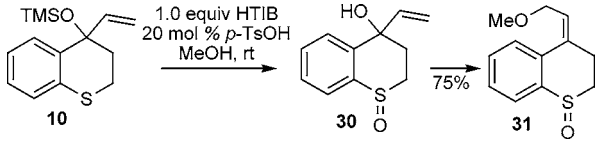
The reactivity of heterocyclic substrates was also examined. When compound **9** was treated with HTIB, the ring expansion reaction also took place. However, an inseparable mixture of the seven-membered ring *O*-heterocycles **27**, **28**, and **29** was isolated (Scheme 7).[11] The oxygen at the ortho position of the migrating carbon appears to somehow change the reactivity.

Treatment of the sulfur derivative **10** with HTIB gave exclusively the sulfoxide **31**, in 75% yield.[11] The first reaction is the oxidation of the sulfide moiety to the corresponding sulfoxide.[17] This electron-withdrawing group would decrease the migratory aptitude of the migrating carbon. Thus, the S_N2' reaction would take place exclusively on **30** (Scheme 8).

Scheme 7. Iodine(III)-Mediated Oxidation of **9**



Scheme 8. Tandem I(III)-Oxidation/S_N2' Reaction of **10**



In conclusion, a metal-free approach for the synthesis of seven- and eight- membered rings through an iodine(III)-mediated ring expansion reaction was described. The substrates can be easily obtained from readily available starting materials. The amount of the oxidizer and the reaction conditions can be managed to obtain different products. Moreover, a short route to the synthesis of medium-ring lactones was developed. The results herein described have great potential for application in the total synthesis of natural products and compounds with biological activity.

Acknowledgment. We thank FAPESP and CNPq for financial support and Prof. Aguilar and Dr. Vieira for discussion.

Supporting Information Available: Spectroscopic and crystallographic data and experimental procedures. This material is available free of charge via the Internet at http://pubs.acs.org.

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(16) The relative configuration of **24** was assigned based on NMR data of related compounds: Tankrad, M. H.; Whitehurst, J. S. *Tetrahedron* **1974**, *30*, 451.

(17) Liu, P.; Liu, S. J.; Zhang, J. Z.; Tian, G. R. *Synth. Commun.* **2005**, *35*, 3173.