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An expeditious synthesis of hexahydrobenzo[*f*]isochromenes and of hexahydrobenzo[*f*]isoquinoline via iodine-catalyzed Prins and aza-Prins cyclization

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ABSTRACT

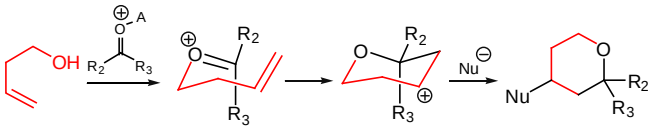
Homoallylic alcohols (primary, secondary, or tertiary containing an endocyclic or an exocyclic double bond) react with equimolar amounts of aldehydes (aliphatic or aromatic) and ketones (aliphatic) in the presence of 5 mol % of iodine. This Prins cyclization was used in the preparation of hexahydrobenzo[*f*]isochromenes and of a 4-hydroxy-tetrahydropyran, in 54–81% yield. The procedure is also efficient for an aza-Prins cyclization of a homoallylic sulfonamide and benzaldehyde, producing a hexahydrobenzo[*f*]isoquinoline.

Hydropyrans are the core of several compounds with biological activity.[1] Among them are included hexahydrobenzo[*f*]isochromenes, such as the biologically active populene D.[2a] Their aza analogues, that is, hexahydrobenzo[*f*]isoquinolines, are CNS active.[2b,c]

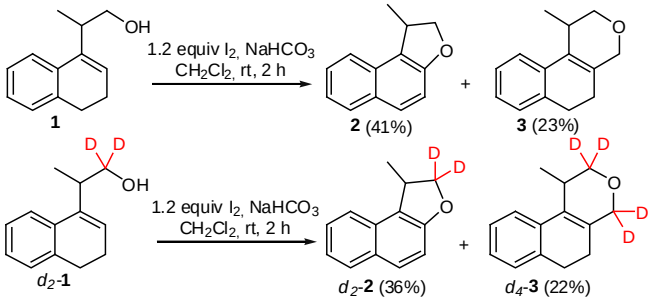
The Prins cyclization constitutes one of the most efficient and widely used methods to diastereoselectively obtain hydropyrans.[3] Thus, Prins cyclization was employed in the key step of several total syntheses of natural products.[4] Moreover, this reaction has been used in macrocyclizations,[4c,d] and in cascade reactions, such as Mukayama Aldol Prins[4e] and Pinacol Prins.[4g] A highly used approach to perform Prins cyclization is the reaction of a homoallylic alcohol with a carbonyl compound in the presence of a Brønsted or a Lewis acid (Scheme 1). The described protocols have at least one of the following limitations: (i) The use of stoichiometric amounts (or excess) of acids,[5a,b] of transition metal salts,[5c] or of an additive, such as TMSCl;[5e] (ii) The homoallylic alcohol or the aldehyde is used in excess;[4a,5,6] (iii) The reaction requires anhydrous conditions and/or inert atmosphere;[4,5] and (iv) only aldehydes can be used as the carbonyl component.[6]

Iodine is a readily available, non-toxic, cheap, and easily manipulated reagent.[7] Prins cyclization can be induced by treating aldehydes[8] or ketones[6a] with 2 equiv of homoallylic alcohols bearing an exocyclic double bond, in the presence of 1 equiv of I_2. Aza-Prins cyclizations[9] can also be induced by I_2 in the presence of GaI_3, producing piperidines.[9e] Herein, we describe that new hexahydrobenzo[*f*]isochromenes can be obtained through a novel protocol for the Prins cyclization, which uses 5 mol % of iodine and equimolar amounts of homoallylic alcohols and carbonyl compounds (aldehydes and ketones). Anhydrous conditions and inert atmosphere are not required. To the best of our knowledge, the Prins cyclization has never been performed with homoallylic alcohols bearing an endocyclic double bond and using catalytic amounts of I_2.

We have been investigating the reactivity of homoallylic alcohols, such as **1**, with Tl(III) salts for several years.[10] These 3-alkenols led to rearrangement products when primary and secondary alcohols were used as substrates.[10a,c] Tertiary ones give rearrangement products or fragmentation products, depending on their



Scheme 1.



Scheme 2.

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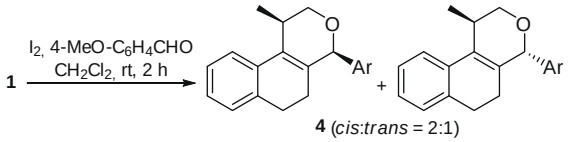
structure.[10b] For all substrates investigated, the cyclization product has never been isolated. In an effort to produce cyclic ethers from **1**, we decided to study its reaction with I_2. Treatment of this homoallylic alcohol with I_2, in the presence of $NaHCO_3$ gave the naphthalene analogue **2** and the hexahydrobenzo[*f*]chromene **3**, respectively (Scheme 2). The compound **2** would be formed from an overall 5-*endo*-*trig* iodocyclization,[11] followed by aromatization. The formation of **3** intrigued us due to the incorporation of an additional CH_2 unit. The fragmentation of homoallylic alcohols has been observed with I_2,[11d] Pb(IV),[12a,b] Tl(III),[10b,12c,d] and other halogens.[12f] Based on that, we envisioned that **3** would be originated by an I_2-induced fragmentation of **1**, generating formaldehyde and other products. The formaldehyde would react with another molecule of **1**, forming **3** via an iodine-promoted Prins cyclization reaction (Scheme 3).[6a,7f,g,8] To support the mechanism, the deuterated compound d_2-**1** was subjected to the same conditions. Analogously to **1**, d_2-**2** and d_4-**3** were obtained (Scheme 2).

Inspired by the formation of **3** from **1**, we decided to investigate the generality of such Prins cyclization. First, the reaction of **1** and *p*-anisaldehyde was carefully studied. The use of 1.1 equiv of I_2 and excess of *p*-anisaldehyde (2.3 equiv) gave the compound **4** as a mixture of diastereomers (cis:trans = 2:1) in 54% yield and 31% of the aldehyde was recovered (Table 1, entry 1). Reducing the amount of I_2 to 0.5 equiv produced **4** in 71% yield in a more clean reaction (entry 2). Reacting **1** with an equimolar amount of aldehyde and with 0.2 equiv of I_2 led to **4** in 81% yield (entry 3). With only 5 mol % of I_2, the yield was 75% (entry 4). Without I_2, **1** was recovered after 20 h (entry 5). The reaction of HI and HOI, which are formed in the reaction medium, gives I_2 and H_2O, explaining the catalytic use of I_2. The iodine(III) reagents PhI(OH)(OTs) (HTIB) and $PhI(OAc)_2$ (DIB) were tested. HTIB produced **4** in 26% yield (entry 6), whereas DIB failed to give the desired product (entry 7). Using TsOH, **4** was formed in 24% yield (entry 8), suggesting that the Brønsted acid character of HTIB is responsible for the reaction and not the presence of the I(III) atom. In summary, the best condition for the Prins cyclization of **1** is using 5 mol % of I_2 and an equimolar amount of aldehyde. This protocol was employed to study the scope of the reaction.

When benzaldehyde was reacted with **1** and 5 mol % of I_2, **5** was obtained as a mixture of diastereomers (cis:trans = 8:1), in 77% yield (Table 2, entry 1). Under similar conditions, 4-nitrobenzaldehyde afforded **6**, as a single diastereomer in 68% yield (entry 2). Iodine induced the depolymerization of paraformaldehyde and subsequently the Prins cyclization of the formaldehyde formed in situ with **1**, affording **3** in 54% yield (entry 3). Acetaldehyde gave **7**, in 78% yield (entry 4). The relatively hindered *t*-BuCHO led to a mixture of **8** and **9** (3:2) in 65% yield (entry 5).

Table 1
I_2-promoted Prins cyclization of **1** and *p*-anisaldehyde[a]



4 (*cis*:*trans* = 2:1)

Entry	*p*-anisaldehyde (equiv)	I_2 (equiv)	Yield of **4** (%)
1	2.3	1.1	54[b]
2	2.1	0.5	71[c]
3	1.0	0.2	81
4	1.0	0.05	75
5	1.0	0	—[d]
6	1.0	HTIB (0.05)	26
7	1.0	DIB (0.10)	—[d]
8	1.0	TsOH (0.10)	24

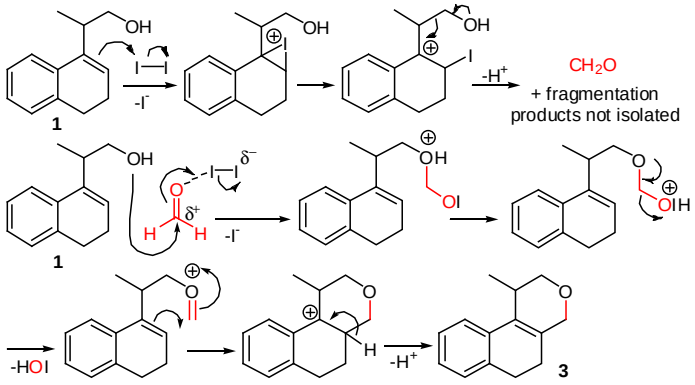
[a] Ratio determined by NMR. Relative configuration assigned by NOESY.
[b] Aldehyde recovered: 31%.
[c] Aldehyde recovered: 67%.
[d] No reaction.

The results of Table 2 can be explained by the following mechanism. Two pathways are possible from the oxonium intermediate **10**. If a transition state like **11** occurs, the carbocation **12** would be formed, leading to *cis*-**4**–**8**. Otherwise, the less stable transition state **13** would lead to **14**, that produces the compounds *trans*-**4,5**. The transition state **13** is more energetic than **11** because of the repulsive interaction between the Me group and H_{10}.[10a] The energy of the oxonium **10** presumably increases along the series R = 4-MeO–C_6H_4, Ph and 4-NO_2–C_6H_4. The formation of the trans diastereomers is disfavored as the energy of **10** increases. Nevertheless, when R = *t*-Bu in **12** or **14**, H_1 is lost, producing **9** that has a different pattern of insaturation than **8**, formed by the exit of H_{4a} (Scheme 4).

After studying the Prins cyclization of various aldehydes, we investigated the behavior of ketones. Acetone reacts with **1** in the presence of 5 mol % of I_2 leading to **15** in 76% yield. The cyclic ether **15** was obtained in gram scale and has a structure analogous to Populene D[2a] (Scheme 5).

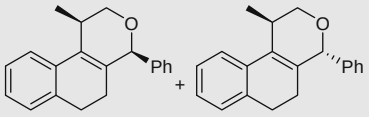
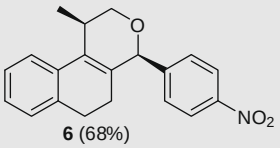
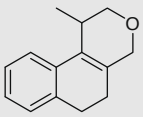
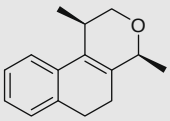
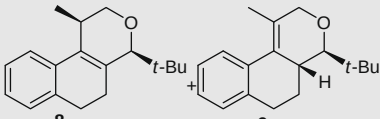
The Prins cyclization of **1** and the cyclic ketones cyclo-pentanone, -hexanone, and -heptanone proved to be efficient in the preparation of the spiro compounds **16**–**18** in 67–77% yield, showing that ring size has minor influence over the reaction (Table 3).

Once the Prins cyclization of **1** with different carbonyl compounds was successfully performed, we check if other homoallylic alcohols could be used. First, the influence of steric effects on the alcohol moiety was investigated. Thus, the tertiary alcohol **19**



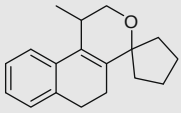
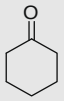
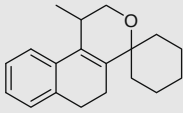
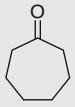
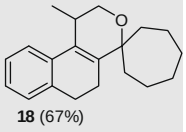
Scheme 3.

Table 2
Reaction of **1** and aliphatic and aromatic aldehydes[a]

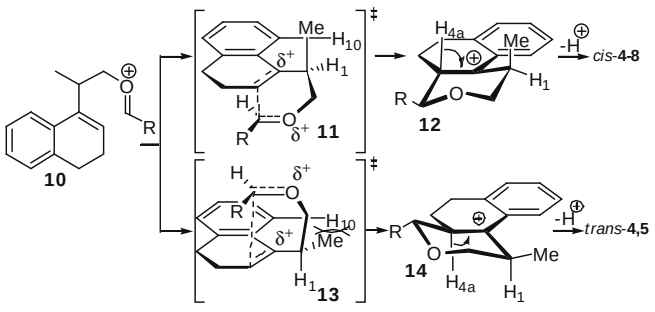
Entry	Aldehyde	Product[b] (yield)
1	PhCHO	 **5** (77%, *cis*:*trans*, 8:1)
2	4-$NO_2C_6H_4CHO$	 **6** (68%)
3	$(CH_2O)_n$	 **3** (54%)
4	MeCHO	 **7** (78%)
5	*t*-BuCHO	 **8** **9** (65%, 3:2)

[a] Aldehyde (1.0 equiv), I_2 (5 mol %), CH_2Cl_2, 2 h.
[b] Ratios obtained by NMR. Relative configuration of compounds **5**–**8** assigned comparing their NMR data to those of **4**. Relative configuration of **9** assigned by NMR.

Table 3
I_2-Catalyzed Prins cyclization of cyclic ketones[a]

Entry	Ketone	Product (yield)
1		 **16** (77%)
2		 **17** (74%)
3		 **18** (67%)

[a] Conditions: ketone (1.0 equiv), I_2 (5 mol %), CH_2Cl_2.

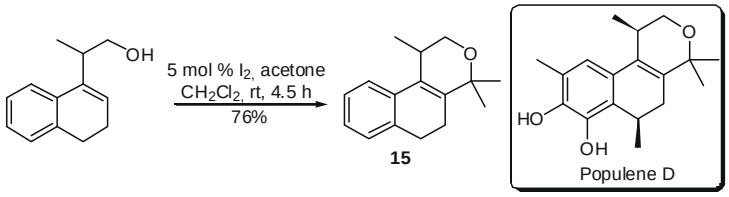


Scheme 4.

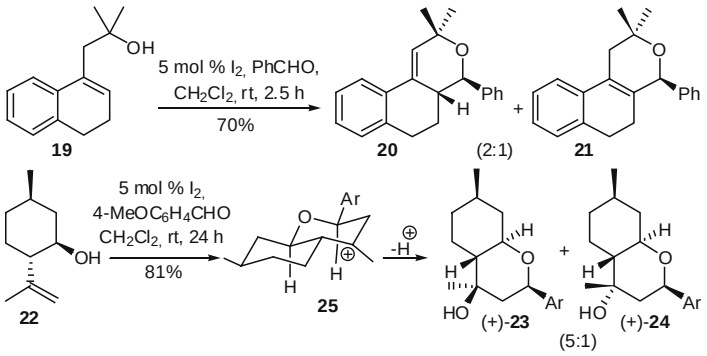
was subjected to the reaction with PhCHO. Analogously to the reaction of **1** and *t*-BuCHO, a mixture of **20** and **21** (2:1) was obtained in 70% yield. We also tested the reactivity of a homoallylic alcohol with an exocyclic insaturation. To this end, we selected the monoterpene (−)-isopulegol (**22**), which was reacted with *p*-anisaldehyde in the presence of I_2, furnishing a mixture of **23** and **24** (5:1),[13] which are formed by the addition of H_2O to the carbocation **25** (Scheme 6). The favored formation of **23** over **24** agrees to Alder's rule.[14] It is important to mention that the Prins cyclization of **22** does not occur through a benzylic carbocation, as the other examples.

Considering that the I_2-catalyzed Prins cyclization was efficiently carried out, we decided to study the analogous aza version. The protocol was tested for the sulfonamide **26** and benzaldehyde. Unfortunately, even after 6 days, 5 mol % of I_2 was unable to produce **27**. However, 20 mol % of I_2 gave **27** in 60% yield. The formation of the trans diastereomer is favored in the aza-Prins, contrasting with the Prins cyclization (compare Table 1 and Scheme 7). The analogous transition states of **11** in the aza-Prins cyclization would be the iminiums *E*-**27** and *Z*-**28**, which would lead to *trans*-**27** and *cis*-**27**, respectively. The steric interactions between Ar and Ts in *Z*-**28** would decrease the formation of *cis*-**26**. The crowded transition state also explains the longer reaction time observed for the reaction of **26**, when compared to **1** (72 vs 2 h). The aza-Prins cyclization of an analogous homoallylic amine and aldehydes and ketones was described using anhydrous TFA as solvent. Compound **27** is analogous to CNS active isoquinolines.[2b,c]

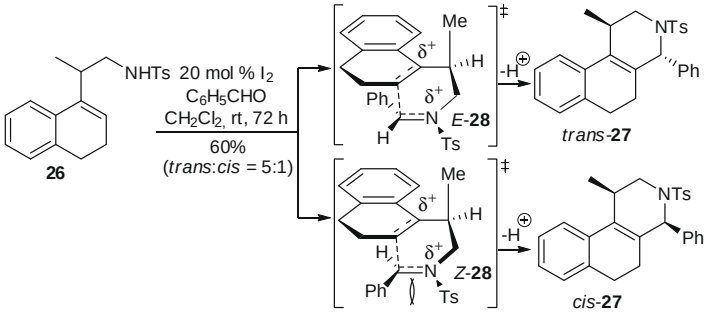
In conclusion, an iodine-catalyzed method for the Prins cyclization was developed. The reaction tolerates different carbonylic



Scheme 5.



Scheme 6.



Scheme 7.

compounds and homoallylic alcohols, which were used in equimolar amounts. Furthermore, the aza-Prins version occurs under analogous conditions. Thus, an expeditious entry toward new hexahydrobenzo[*f*]-chromenes and hexahydrobenzo[*f*]isoquinoline has been disclosed. Additional studies for these Prins and aza-Prins cyclizations are being developed in our group.

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Supplementary data

Spectroscopic data and experimental procedures are available. Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2009.02.202.

References and notes

1. For examples of biologically active compounds bearing a hydropyran unit, see: (a) MacMillan, J. B.; Zhou, G. X-.; Skepper, C. K.; Molinski, T. F. *J. Org. Chem.* **2008**, *73*, 3699; (b) Wright, A. E.; Botelho, J. C.; Guzman, E.; Harmody, D.; Linley, P.; McCarthy, P. J.; Pitts, T. P.; Pomponi, S. A.; Reed, J. K. *J. Nat. Prod.* **2007**, *70*, 412; (c) Searle, P. A.; Molinski, T. F. *J. Am. Chem. Soc.* **1995**, *117*, 8126.
2. (a) Boonsri, S.; Karalai, C.; Chantrapromma, S.; Kanjana-opas, A. *J. Nat. Prod.* **2008**, *71*, 1173; (b) Ménard, M.; Rivest, P.; Morris, L.; Meunier, J.; Perron, Y. G. *Can. J. Chem.* **1974**, *52*, 2316; (c) Wu, X.; Chen, J.; Ji, M.; Levant, B.; Wang, S. *Bioorg. Med. Chem.* **2000**, *14*, 5813.
3. For reviews regarding Prins reaction and Prins cyclization, see: (a) Pastor, I. M.; Yus, M. *Curr. Org. Chem.* **2007**, *11*, 925; (b) Vasconcellos, M. L. A. A.; Miranda, L. S. M. *Quim. Nova* **2006**, *29*, 834; (c) Clarke, P. A.; Santos, S. *Eur. J. Org. Chem.* **2006**, 2045; (d) Adams, D. R.; Bhatnagar, S. P. *Synthesis* **1977**, 661; (e) Arundale, E.; Mikeska, L. A. *Chem. Rev.* **1952**, *51*, 505.
4. For examples, see: (a) Vintonyak, V. V.; Kunze, B.; Sasse, F.; Maier, M. E. *Chem. Eur. J.* **2008**, *14*, 11132; (b) Seden, P. T.; Charmant, J. P. H.; Willis, C. L. *Org Lett.* **2008**, *10*, 1637; (c) Woo, S. K.; Kwon, M. S.; Lee, E. *Angew. Chem., Int. Ed.* **2008**, *47*, 3242; (d) Bahnck, K. B.; Rychnovsky, S. D. *J. Am. Chem. Soc.* **2008**, *130*, 13177; (e) Kopecky, D. J.; Rychnovsky, S. D. *J. Am. Chem. Soc.* **2001**, *123*, 8420; (f) Van Orden, L. J.; Patterson, B. D.; Rychnovsky, S. D. *J. Org. Chem.* **2007**, *72*, 5784; (g) Overman, L. E.; Pennington, L. D. *J. Org. Chem.* **2003**, *68*, 7143.
5. (a) Jasti, R.; Rychnovsky, S. D. *J. Am. Chem. Soc.* **2006**, *128*, 13640; (b) Hiebel, M.; Pelotier, B.; Piva, O. *Tetrahedron* **2007**, *63*, 7874; (c) Cheung, L. L.; Marumoto, S.; Anderson, C. D.; Rychnovsky, S. D. *Org. Lett.* **2008**, *10*, 3101; (d) Tadpetch, K.; Rychnovsky, S. D. *Org. Lett.* **2008**, *10*, 4839; (e) Miranda, P. O.; Carballo, R. M.; Martín, V. S.; Padrón, J. I. *Org. Lett.* **2009**, *11*, 357.
6. Few examples were reported using ketones: (a) Yadav, J. S.; Reddy, B. V. S.; Krishna, V. H.; Swamy, T.; Kumar, G. G. K. S. *Can. J. Chem.* **2007**, *85*, 412. and references therein; (b) Miles, R. B.; Davis, C. E.; Coates, R. M. *J. Org. Chem.* **2006**, *71*, 1493.
7. For recent reviews concerning iodine, see: (a) Stavber, S.; Jereb, M.; Zupan, M. *Synthesis* **2008**, 1487; (b) Togo, H.; Iida, S. *Synlett* **2006**, 2159; (c) Smith, M. B. *e-EROS Encyclopedia of Reagents for Organic Synthesis*; John Wiley & Sons, Ltd, 2001; (d) French, A. N.; Bissmire, S.; Wirth, T. *Chem. Soc. Rev.* **2004**, *33*, 354; (e) Das, S.; Borah, R.; Devi, R. R.; Thakur, A. J. *Synlett* **2008**, 2741; For some reactions using iodine as Lewis acid, see: (f) Sun, J.; Dong, Y.; Cao, L.; Wang, X.; Wang, S.; Hu, Y. *J. Org. Chem.* **2004**, *69*, 8932; (g) Bosco, J. W. J.; Agrahari, A.; Saikia, A. K. *Tetrahedron Lett.* **2006**, *47*, 4065.
8. Yadav, J. S.; Reddy, B. V. S.; Kumar, G. G. K. S. N.; Swamy, T. *Tetrahedron Lett.* **2007**, *48*, 2205.
9. For selected recent examples, see: (a) Kishi, Y.; Nagura, H.; Inagi, S.; Fushigami, T. *Chem. Commun.* **2008**, 3876; (b) Armstrong, A.; Bhonoah, Y.; Shanahan, S. *J. Am. Chem. Soc.* **2007**, *72*, 8019; (c) Carballo, R. M.; Ramírez, M. A.; Rodríguez, M. L.; Martín, V. S.; Padrón, J. I. *Org. Lett.* **2006**, *8*, 3837; (d) Cesati, R. R., III; Katzenellenbogen, J. *Org. Lett.* **2000**, *2*, 3635; (e) Yadav, J. S.; Reddy, B. V. S.; Chaya, D. N.; Kumar, G. G. K. S. N.; Aravind, S.; Kunwar, A. C.; Madavi, C. *Tetrahedron Lett.* **2008**, *49*, 3330.
10. (a) Silva, L. F., Jr.; Quintiliano, S. A. P.; Craveiro, M. V.; Vieira, F. Y. M.; Ferraz, H. M. C. *Synthesis* **2007**, 355; (b) Silva, L. F., Jr.; Quintiliano, S. A. P.; Ferraz, H. M. C.; Santos, L. S.; Eberlin, M. N. *J. Braz. Chem. Soc.* **2006**, *17*, 981; (c) Ferraz, H. M. C.; Silva, L. F., Jr. *Tetrahedron* **2001**, *57*, 9939; (d) Silva, L. F.; Craveiro, M. V. *Molecules* **2005**, *10*, 1419.
11. For examples of 5-*endo-trig* iodocyclization, see: (a) Barks, J. M.; Weingarten, G. G.; Knight, D. W. *J. Chem. Soc., Perkin Trans. 1* **2000**, 3469; (b) Bedford, S. B.; Bell, K. E.; Bennett, F.; Hayes, C. J.; Knight, D. W.; Shaw, D. E. *J. Chem. Soc., Perkin Trans. 1* **1999**, 2143; (c) Barks, J. M.; Knight, D. W.; Seaman, C. J.; Weingarten, G. G. *Tetrahedron Lett.* **1994**, *35*, 7259; (d) Knight, D. W. *Prog. Heterocycl. Chem.* **2002**, *14*, 19; Terminal olefins and endocyclic olefins afforded 4-exo-tet iodocyclization products: (e) Galatsis, P.; Parks, D. J. *Tetrahedron Lett.* **1994**, *35*, 6611.
12. (a) Khan, F. A.; Sudheer, C.; Soma, L. *Chem. Commun.* **2007**, 4239–4241; (b) Preite, M. D.; Cuellar, M. A. *Chem. Commun.* **2004**, 1970; (c) Kocovský, P.;

Baines, R. S. *J. Org. Chem.* **1994**, *59*, 5439; (d) Kocovský, P.; Langer, V.; Gogoll, A. *J. Chem. Soc., Chem. Commun.* **1990**, 1026; (e) Yadav, J. S.; Patil, D. G.; Krishna, R. R.; Chawla, H. P. S.; Dev, S. *Tetrahedron* **1982**, *38*, 1003; (f) Yadav, J. S.; Chawla, H. P. S.; Dev, S. *Tetrahedron Lett.* **1977**, *2*, 201.

13. The relative configuration of **23** and **24** was assigned by comparison to the NMR data of other 4-hydroxy-tetrahydropyrans. Abate, A.; Allievi, M.; Brenna, E.; Fuganti, C.; Gatti, F. G.; Serra, S. *Helv. Chim. Acta* **2006**, *89*, 177.
14. Alder, R. W.; Harvey, J. N.; Oakley, M. T. *J. Am. Chem. Soc.* **2002**, *124*, 4960.