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Synthesis of Tetrahydrofurans by Cyclization of Homoallylic Alcohols with Iodine/Iodine(III)

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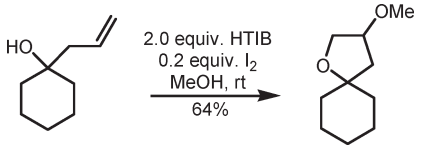

Tetrahydrofuran derivatives can be obtained by cyclofunctionalization of homoallylic alcohols bearing a terminal double bound by using [hydroxy(tosyloxy)iodo]-benzene (HTIB, Koser's reagent) in the presence of a catalytic amount of I_2 (20 mol %) in MeOH under mild conditions. This transformation is an overall 5-*endo*-*trig* cyclization, which occurs by two different pathways. The first is a 4-*exo*-*trig* cyclization followed by ring expansion, whereas the second is an electrophilic addition followed by a 5-*endo*-*tet* cyclization.

The tetrahydrofuran moiety is present in several molecules with biological activity, including important natural products.[1] Thus, a plethora of different methods have been developed to obtain this structural motif.[1] One of them is the cyclofunctionalization of unsaturated alcohols mediated by electrophiles.[1] Appropriate substrates to obtain functionalized tetrahydrofurans are homoallylic alcohols, whose cyclofunctionalization has been investigated by using different electrophiles, such as halogens, iodine(III), thallium(III), mercury(II), etc.[1] However, the iodocyclization of homoallylic alcohols bearing a terminal double bond leads to four-membered-ring derivatives or to complex mixtures,[1,2] because the 5-*endo*-*trig* cyclization that would deliver tetrahydrofuran derivatives is not favored according to the Baldwin's rules and the 4-*exo*-*trig* mode takes place. Fragmentation reactions may also take place when 3-alkenols are treated with halogens.[3]

Hypervalent iodine reagents constitute a class of reagents that can be used for a number of oxidative transformations with a high level of selectivity, constituting an alternative to toxic heavy metals.[4] Although the cyclization of unsaturated carboxylic acids with I(III) has been described in several papers,[5] there are not many reports of the corresponding reaction with unsaturated alcohols.[6] Herein, we describe the synthesis of diverse tetrahydrofurans from readily available homoallylic alcohols bearing a terminal double bond using I(III) in the presence of I_2. This transformation represents a formal 5-*endo*-*trig* cyclization, for which a mechanism is proposed based on isolated intermediates.

The preparation of the required homoallylic alcohols **1a**−**k** was performed by reacting ketones with allyl magnesium bromide, except for substrate **1g**, which was prepared from 4-phenylcyclohexanone with Zn/allyl bromide. Considering our previous experience in the reaction of unsaturated alcohols with HTIB,[7] the first substrate studied was **1a**, which was treated with HTIB under different conditions. The reaction of **1a** with HTIB in MeOH or in MeCN led to products of substitution (**2**) or elimination (**3**), respectively, of the tertiary alcohol, without reaction at the double bond (Scheme 1). These transformations presumably occur through the formation of a benzylic carbocation, due to

(1) Reviews: (a) Boivin, T. L. B. *Tetrahedron* **1987**, *43*, 3309. (b) Cardillo, G.; Orena, M. *Tetrahedron* **1990**, *46*, 3321. (c) Harmange, J.-C.; Figadère, B. *Tetrahedron* **1993**, *4*, 1711. (d) French, A. N.; Bissmire, S.; Wirth, T. *Chem. Soc. Rev.* **2004**, *33*, 354. (e) da Silva, F. M.; Jones, J.; de Mattos, M. C. S. *Curr. Org. Synth.* **2005**, *2*, 393. (f) Togo, H.; Iida, S. *Synlett* **2006**, 2159. (g) Wolfe, J. P.; Hay, M. B. *Tetrahedron* **2007**, *63*, 261. (h) Jalce, G.; Franck, X.; Figadére, B. *Tetrahedron: Asymmetry* **2009**, *20*, 2537. (i) Silva, L. F., Jr.; Carneiro, V. M. T. *Synthesis* **2010**, 1059.

(2) Examples: (a) Evans, R. D.; Magee, J. W.; Schauble, J. H. *Synthesis* **1988**, 862. (b) Galatsis, P.; Parks, D. J. *Tetrahedron Lett.* **1994**, *35*, 6611. (c) Galatsis, P.; Millan, S. D.; Ferguson, G. *J. Org. Chem.* **1997**, *62*, 5048. (d) Wang, G.; Wang, Y.; Arcari, J. T.; Howell, A. R.; Rheingold, A. L.; Concolino, T. *Tetrahedron Lett.* **1999**, *40*, 7051. (e) 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. (f) Rofoo, M.; Roux, M.-C.; Rousseau, G. *Tetrahedron Lett.* **2001**, *42*, 2481. (g) Robin, S.; Rousseau, G. *Eur. J. Org. Chem.* **2002**, 3099.

(3) Examples: (a) Yadav, J. S.; Chawls, H. P. S.; Dev, S. *Tetrahedron Lett.* **1977**, 201. (b) Yadav, J. S.; Patil, D. G.; Krishna, R. R.; Chawla, H. P. S.; Dev, S. *Tetrahedron* **1982**, *38*, 1003. (c) Silva, L. F., Jr.; Quintiliano, S. A. P. *Tetrahedron Lett.* **2009**, *50*, 2256.

(4) Selected recent reviews: (a) Varvoglis, A. *Hypervalent Iodine in Organic Synthesis*; Academic Press: London, UK, 1997. (b) Koser, G. F. *Aldrichim. Acta* **2000**, *34*, 89. (c) *Hypervalent Iodine Chemistry*; Wirth, T., Ed.; Springer: Berlin, Germany, 2003. (d) Moriarty, R. M. *J. Org. Chem.* **2005**, *70*, 2893. (e) Silva, L. F., Jr. *Molecules* **2006**, *11*, 421. (f) Ciufolini, M. A.; Braun, N. A.; Canesi, S.; Ousmer, M.; Chang, J.; Chai, D. *Synthesis* **2007**, *24*, 3759. (g) Zhdankin, V. V.; Stang, P. J. *Chem. Rev.* **2008**, *108*, 5299. (h) Merritt, E. A.; Olofsson, B. *Angew. Chem., Int. Ed.* **2009**, *48*, 9052. (i) Pouységu, L.; Deffieux, D.; Quideau, S. *Tetrahedron* **2010**, *66*, 2235.

(5) Examples: (a) Shah, M.; Taschner, M. J.; Koser, G. F.; Rach, N. L.; Jenkins, T. E.; Cyr, P.; Powers, D. *Tetrahedron Lett.* **1986**, *27*, 5437. (b) Shah, M.; Taschner, M. J.; Koser, G. F.; Rach, N. L. *Tetrahedron Lett.* **1986**, *27*, 4557. (c) Koser, G. F.; Lodaya, J. S.; Ray, D. G.; Kokil, P. B. *J. Am. Chem. Soc.* **1988**, *110*, 2987. (d) Boye, A. C.; Meyer, D.; Ingison, C. K.; French, A. N.; Wirth, T. *Org. Lett.* **2003**, *5*, 2157. (e) Liu, H.; Tan, C.-H. *Tetrahedron Lett.* **2007**, *48*, 8220. (f) Yan, J.; Wang, H.; Yang, Z.; He, Y. *Synlett* **2009**, 2669. (g) Uyanik, M.; Yasui, T.; Ishihara, K. *Bioorg. Med. Chem. Lett.* **2009**, *19*, 3848. (h) Uyanik, M.; Yasui, T.; Ishihara, K. *Angew. Chem., Int. Ed.* **2010**, *49*, 2175. (i) Uyanik, M.; Yasui, T.; Ishihara, K. *Tetrahedron* **2010**, *66*, 5841.

(6) Examples: (a) Kim, H.-j.; Schlecht, M. F. *Tetrahedron Lett.* **1987**, *28*, 5229. (b) Sawaguchi, M.; Hara, S.; Fukuhara, T.; Yoneda, N. *J. Fluorine Chem.* **2000**, *104*, 277. (c) Giannis, A.; Heretsch, P.; Sarli, V.; Stossel, A. *Angew. Chem., Int. Ed.* **2009**, *48*, 7911. (d) Uyanik, M.; Okamoto, H.; Yasui, T.; Ishihara, K. *Science* **2010**, *328*, 1376.

(7) Silva, L. F., Jr.; Vasconcelos, R. S.; Nogueira, M. A. *Org. Lett.* **2008**, *10*, 1017.

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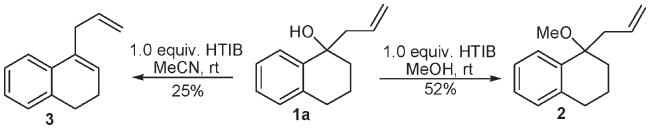
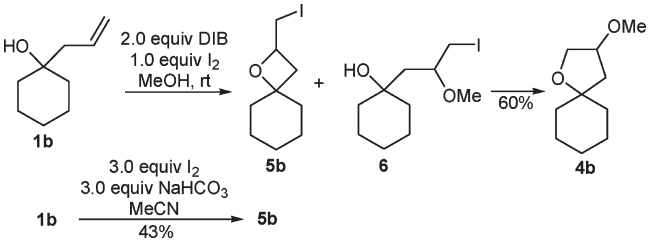
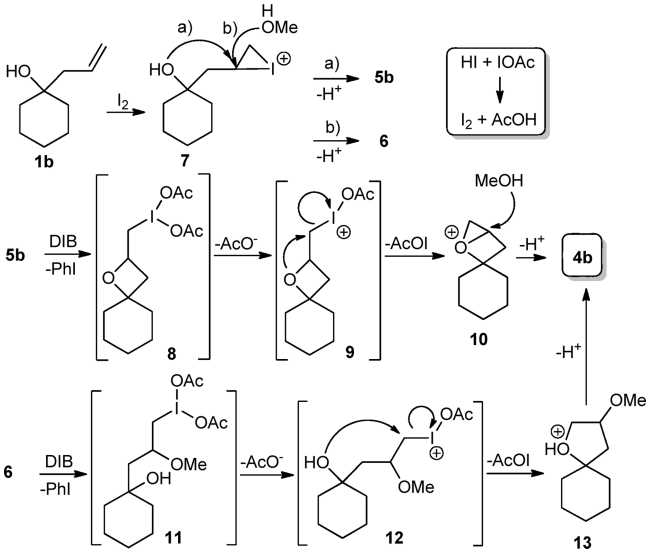
SCHEME 1. Reaction of 1a with HTIB



SCHEME 2. Cyclization Reactions of 1b



SCHEME 3. Mechanisms for the Cyclization of 1b with I_2/DIB



the acidic medium. When **1a** was exposed to HTIB in the presence of base (1 equiv of HTIB, 2.4 equiv of $NaHCO_3$, MeOH, rt), no reaction was observed even after 4 days. An analogous result was observed by treating **1a** with diacetoxyiodobenzene (DIB) under several conditions.[8]

After these disappointing initial results and inspired by previous works,[9,10] we decided to investigate the reaction of homoallylic alcohols with the combination I(III)/I_2. For these tests, the substrate **1b** was selected, which would be less prone to carbocation formation than **1a**. Gratefully, the reaction of **1b** with DIB and I_2 gave the tetrahydrofuran **4b** in 60% yield. The course of this cyclization was monitored by TLC analysis. Initially, alkenol **1b** originated two different compounds (oxetane **5b** and iodide **6**), which led to the desired cyclic ether **4b** as time progressed. Interrupting the reaction in the beginning, the reaction intermediates **5b** and **6** were isolated. In striking contrast, treatment of **1b** with I_2 under classical cyclization conditions gave only the oxetane **5b** (Scheme 2). We proposed a mechanism for the formal 5-*endo*-*trig* cyclization of **1b**, which relays mainly on oxidative displacement of iodine from alkyl iodides[11] and the ring expansion of cyclic ethers having an iodoalkyl substituent[12,13] that were both described with use of I(III). These reactions are possible due to the oxidation of an alkyl iodide to the corresponding I(III) species, which is a hypernucleofuge.[14] Thus, first I_2 would attack the double bond of alcohol **1b**. Iodonium ion **7** has two pathways to follow. In route a, the formation of the oxetane **5b** would take place by a 4-*exo*-*trig* process in **7**. Then, oxetane **5b** would be oxidized to the unstable alkyl I(III) species **8**, which is prone to formation of the bicyclic oxonium ion **10**, by the displacement of the hypervalent iodine group by oxygen. MeOH would add to oxonium **10** producing **4b**,[15] after deprotonation. In route b, the methoxy alkyl iodide **6** would be formed by addition of MeOH to the iodonium ion **7**. Oxidation of the iodide group of **6** could convert it into a hypernucleofuge (**11**). The intramolecular attack of the hydroxy group to the I(III) moiety of **12** would displace the iodine group leading to **13**, through a 5-*exo*-*tet* process (Scheme 3).

The reaction scope was then investigated. As shown in Table 1 (entries 1−9), substituted tetrahydrofurans bearing a spiro cyclic unit were obtained in moderate to good yield. On the other hand, the substrate **1k** gave only the oxetane **5k** (entry 10). Moreover, the unsaturated alcohol **1a** led to a complex mixture under similar conditions. During the optimization process, we found that higher yields of the desired product are obtained with HTIB instead of DIB. Additionally, this modification decreased reaction times and the amount of hypervalent iodine and I_2 (cf. entries 1, 4, and 7). The alcohol moiety of the substrate can be either in cyclic (cf. entries 1−3, 5−8) or in acyclic (cf. entries 4 and 9) systems. The diastereoselectivity observed in the cyclization of **1h**−**j** (entries 7−9) is low to moderate. However, this selectivity is higher than that observed in similar reactions.[16] The transformation of homoallylic alcohols into spirocyclic ethers analogous to **4** has been reported by using, for example, Pd(II)/DIB;[16] $NaIO_4$:$NaHSO_3$;[17] epoxidation followed acid hydrolysis/cyclization;[18] and bromine addition followed by treatment with base.[19] Compared to these previous works, the present methodology has the advantage to be one step, metal-free, and of simple operation. As MeOH is incorporated in the final product, we expected that different tetrahydrofuran derivatives would be obtained changing the

(8) Conditions tested were the following: (a) 1 equiv of DIB, MeOH, rt, 30 min; (b) 1 equiv of DIB, MeCN, rt (3 d), reflux (7 h); (c) 1 equiv of DIB, 3.0 equiv of KOH, MeOH, rt, 4 d.

(9) Djuardi, E.; Mc Nelis, E. *Tetrahedron Lett*. **1999**, *40*, 7193.

(10) Herault, X.; McNelis, E. *Tetrahedron* **1996**, *52*, 10267.

(11) Gallos, J.; Varvoglis, A. *J. Chem. Soc., Perkin Trans. 1* **1983**, 1999.

(12) Abo, T.; Sawaguchi, M.; Senboku, H.; Hara, S. *Molecules* **2005**, *10*, 183.

(13) Inagaki, T.; Nakamura, Y.; Sawaguchi, M.; Yoneda, N.; Ayuba, S.; Hara, S. *Tetrahedron Lett*. **2003**, *44*, 4117.

(14) It was estimated that the I(III) is a better leaving group than I by a factor of 10^{13-14}. For a discussion, see: Ochiai, M. Reactivities, Properties and Structures, in Hypervalent Iodine Chemistry: Modern Developments in Organic Synthesis. *Top. Curr. Chem*. **2003**, 5–68.

(15) Ferraz, H. M. C.; Ribeiro, C. M. R.; Grazini, M. V. A.; Brocksom, T. J.; Brocksom, U. *Tetrahedron Lett*. **1994**, *35*, 1497.

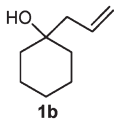
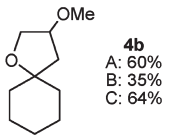
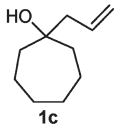
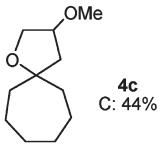
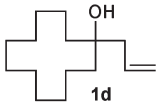
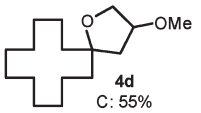
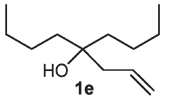
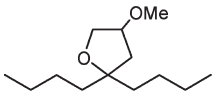
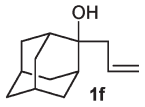
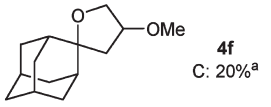
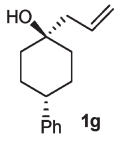
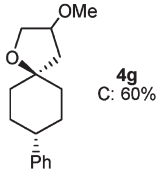
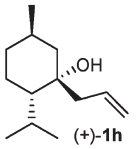
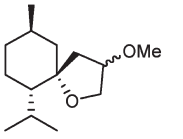
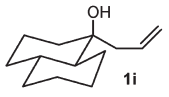
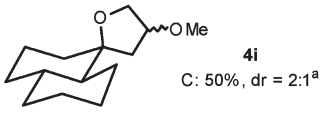
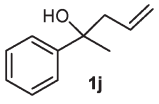
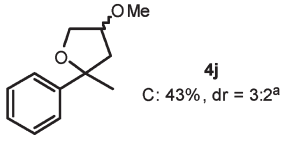
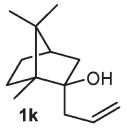
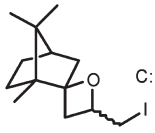
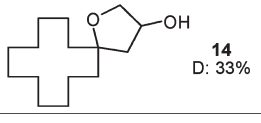
(16) Li, Y.; Song, D.; Dong, V. M. *J. Am. Chem. Soc*. **2008**, *130*, 2962.

(17) Okimoto, Y.; Kikuchi, D.; Sakaguchi, S.; Ishii, Y. *Tetrahedron Lett*. **2000**, *41*, 10223.

(18) Chirskaya, M. V.; Vasil'ev, A. A.; Shorshnev, S. V.; Sviridov, S. I. *Russ. Chem. Bull*. **2006**, *55*, 1300.

(19) Chirskaya, M. V.; Vasil'ev, A. A.; Sergovskaya, N. L.; Shorshnev, S. V.; Sviridov, S. I. *Tetrahedron Lett*. **2004**, *45*, 8811.

TABLE 1. Reaction of 1b−k with I_2/DIB (A and B) or with I_2/HTIB (C)[b]

Entry	Substrate	Product, Yield
1	 **1b**	 **4b** A: 60% B: 35% C: 64%
2	 **1c**	 **4c** C: 44%
3	 **1d**	 **4d** C: 55%
4	 **1e**	 **4e** A: 44% B: 39% C: 47%
5	 **1f**	 **4f** C: 20%[a]
6	 **1g**	 **4g** C: 60%
7	 (+)-**1h**	 **4h** A: 50%, dr = 7:3 B: 31%, dr = 3:2 C: 57%, dr = 1:1[a]
8	 **1i**	 **4i** C: 50%, dr = 2:1[a]
9	 **1j**	 **4j** C: 43%, dr = 3:2[a]
10	 **1k**	 **5k** C: 33%, dr = 3:2
11	**1d**	 **14** D: 33%

[a]3 equiv of HTIB. [b]A: 4 equiv of DIB, 0.5 equiv of I_2, MeOH, rt. B: 4 equiv of DIB, 0.2 equiv of I_2, MeOH, 60−70 °C. C: 2 equiv of HTIB, 0.2 equiv of I_2, MeOH, rt. D: 2 equiv of HTIB, 20 mol % of I_2, CH_3CN/H_2O 4:1, rt, 4 days.

solvent. Indeed, when the reaction was performed in water, the desired hydroxy tetrahydrofuran **14** was obtained. However, the best yield was only 33% yield (entry 11).[20]

In summary, a new protocol to obtain tetrahydrofuran derivatives by treatment of readily available homoallylic alcohols with I(III) in the presence of I_2 under mild conditions was developed. This simple, one-step, and metal-free procedure has great applicability in the synthesis of biologically active natural products. Reaction intermediates were isolated and characterized giving support for two mechanisms. One of them would be a 4-*exo-trig* cyclization followed by ring expansion, whereas the second would be an electrophilic addition followed by 5-*endo-tet* cyclization.

Experimental Section

3-Methoxy-1-oxa-spiro[4,5]decano (4b). To a stirred solution of **1b** (0.035 g, 0.25 mmol) and I_2 (0.013 g, 0.050 mmol) in MeOH (1 mL) at 0 °C was slowly added HTIB (0.196 g, 0.500 mmol). The mixture was stirred for 16 h at rt. The reaction was quenched with a 10% solution of Na_2SO_3 (6 mL) and extracted with EtOAc (4 × 4 mL). The organic phase was washed with a saturated solution of $NaHCO_3$ (4 mL) and brine (4 mL), then dried over anhydrous $MgSO_4$. The solvent was removed under reduced pressure. The crude product was purified by column (10−20% Et_2O in pentane), giving **4b** (0.027 g, 64%) as a colorless oil. IR (film): 2931, 2857, 1448, 1102, 1088, 1071. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.36−1.68 (m, 10H), 1.79 (ddd, J = 0.6, 3.6, 13.4 Hz, 1H), 1.85 (dd, J = 6.0, 13.4 Hz, 1H), 3.27 (s, 3H), 3.83 (ddd, J = 0.6, 3.3, 9.8 Hz, 1H), 3.89 (dd, J = 4.7, 9.8 Hz, 1H), 3.97 (dddd, J = 3.3, 3.6, 4.7, 6.0 Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 23.6, 23.7, 25.5, 37.27, 37.33, 42.5, 56.8, 70.5, 81.9, 82.5. LRMS m/z (%): 170 ($M^{\bullet+}$, 23), 139 (44), 127 (96), 114 (30), 95 (100). HRMS [ESI(+)] calcd for $[C_{10}H_{18}O_2+Na]^+$ 193.11990, found 193.12012.

3-Methoxy-1-oxa-spiro[4,6]undecane (4c). As for **4b**, but with **1c** (0.039 g, 0.25 mmol), I_2 (0.013 g, 0.050 mmol), MeOH (1 mL), HTIB (0.196 g, 0.500 mmol), and 15 h. Purification (10% Et_2O in pentane) gave **4c** (0.020 g, 44%) as a colorless oil. IR (film): 1058, 1078, 1102, 1460, 2857, 2927 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.30−1.44 (m, 2H), 1.46−1.68 (m, 6H), 1.70−1.92 (m, 6H), 3.28 (s, 3H), 3.81 (ddd, J = 0.6, 3.3, 9.8 Hz, 1H), 3.89 (dd, J = 5.0, 9.8 Hz, 1H), 3.95−4.01 (m, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 22.7, 29.11, 29.13, 40.3, 40.6, 44.2, 56.8, 70.6, 81.9, 86.2. LRMS m/z (%) 184 ($M^{\bullet+}$, 35), 153 (48), 141 (73), 127 (100), 109 (25), 95 (89). HRMS [ESI(+)] calcd for $[C_{11}H_{20}O_2 + H]^+$ 185.1536, found 185.1535.

3-Methoxy-1-oxa-spiro[4,11]hexadecane (4d). As for **4b**, but with **1d** (0.056 g, 0.25 mmol), I_2 (0.013 g, 0.050 mmol), MeOH (1 mL), HTIB (0.196 g, 0.500 mmol), and 22 h. Purification (10% EtOAc in hexane) gave **4d** (0.035 g, 55%) as a colorless oil. IR (film): 733, 1074, 1099, 1445, 1471, 2243, 2863, 2934 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.34 (s, 19H), 1.46−1.63 (m, 2H), 1.71−1.76 (m, 1H), 1.76 (dd, J = 3.3, 13.3 Hz, 1H), 1.84 (dd, J = 6.7, 13.3 Hz, 1H), 3.27 (s, 3H), 3.79 (dd, J = 3.2, 9.8 Hz, 1H), 3.91 (dd, J = 5.3, 9.8 Hz, 1H), 4.00 (dddd, J = 3.2, 3.3, 5.3, 6.7 Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 19.9, 22.1, 22.2, 22.45, 22.46, 26.0, 26.43, 26.44, 32.9, 33.3, 42.5, 56.8, 70.7, 82.1, 85.8. LRMS m/z (%): 254 ($M^{\bullet+}$, 44), 223 (90), 183 (48), 127 (100), 95 (90). HRMS [ESI(+)] calcd for $[C_{16}H_{30}O_2 + Na]^+$ 277.21435, found 277.21380.

2,2-Dibutyltetrahydro-4-methoxyfuran (4e). As for **4b**, but with **1e** (0.046 g, 0.25 mmol), I_2 (0.013 g, 0.050 mmol), MeOH (1 mL), HTIB (0.196 g, 0.500 mmol), and 16 h. Purification (10% EtOAc in hexane) gave **4e** (0025 g, 47%) as a colorless oil. IR (film): 1079, 1101, 1195, 1241, 1378, 1466, 1742, 2872, 2932 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.89 (t, J = 7.0 Hz, 6H), 1.19−1.35 (m, 8H), 1.38−1.67 (m, 4H), 1.76 (dd, J = 3.5, 13.3

(20) See the Supporting Information for additional conditions.

Hz, 1H), 1.89 (dd, J = 6.9, 13.3 Hz, 1H), 3.28 (s, 3H), 3.78 (dd, J = 3.5, 9.6 Hz, 1H), 3.90 (dd, J = 5.2, 9.6 Hz, 1H), 3.98 (dddd, J = 3.5, 3.5, 5.2, 6.9 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 14.1, 23.3, 26.4, 26.6, 37.9, 38.1, 41.4, 56.9, 70.9, 81.9, 85.3. LRMS m/z (%): 157 (100), 125 (80). HRMS [ESI(+)] calcd for $[C_{13}H_{26}O_2 + Na]^+$ 237.18305, found 237.18250.

Dihydro-4-methoxyspiro[furan-2(3*H*),2′-tricyclo[3.3.1.13.7]-decane] (4f). As for **4b**, but with **1f** (0.048 g, 0.25 mmol), I_2 (0.013 g, 0.050 mmol), HTIB (0.294 g, 0.750 mmol), MeOH (1 mL), and 41 h. Purification (10−20% EtOAc in hexane) gave **4f** (0.011 g, 20%) as a colorless oil. IR (film): 1099, 1108, 1452, 2853, 2905 cm^{-1}. ^{1}H NMR (200 MHz, $CDCl_3$): δ 1.49−1.97 (m, 14H), 2.10−2.25 (m, 2H), 3.29 (s, 3H), 3.87−4.00 (m, 3H). ^{13}C NMR (50 MHz, $CDCl_3$): δ 26.8, 27.2, 27.8, 33.2, 33.6, 35.4, 35.9, 36.8, 37.1, 37.7, 41.4, 56.8, 70.1, 82.0, 86.4. LRMS m/z (%): 222 ($M^{\bullet+}$, 17), 192 (14), 175 (8), 160 (23), 91 (46), 79 (57), 41 (100). HRMS [ESI(+)] calc for $[C_{14}H_{23}O_2 + H]^+$ 223.1693, found 223.1690.

3-Methoxy-8-phenyl-1-oxaspiro[4,5]decane (4g). As for **4b**, but with **1g** (0.061 g, 0.282 mmol), HTIB (0.221 g, 0.563 mmol), I_2 (0.014 g, 0.056 mmol), MeOH (1.0 mL), and 20 h. Purification (20% Et_2O in hexane) gave **4g** (0.042 g, 60%) as a colorless oil. IR (film): 533, 700, 756, 1046, 1072, 1095, 1108, 1441, 1493, 2858, 2927, 3027, 3060, 3083 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.45−1.57 (m, 2H), 1.68−1.94 (m, 7H), 2.08 (ddd, J = 3.0, 5.9, 13.6 Hz, 1H), 2.48 (tt, J = 3.5, 12.1 Hz, 1H), 3.30 (s, 3H), 3.86−3.96 (m, 2H), 3.98−4.04 (m, 1H), 7.14−7.19 (m, 1H), 7.22−7.30 (m, 4H). ^{13}C NMR (50 MHz, $CDCl_3$): δ 30.2, 30.4, 36.8, 37.1, 43.7, 44.5, 56.8, 70.9, 80.8, 81.7, 125.8, 126.9, 128.2, 147.3. LRMS m/z (%): 246 ($M^{\bullet+}$, 2), 127 (100), 104 (17), 91 (22), 77 (10). HRMS [ESI(+)] calcd for $[C_{16}H_{22}O_2 + Na]^+$ 269.1512, found 269.1510.

(3-*RS*)-(4,5*R*,6*S*,9*R*)-6-Isopropyl-3-methoxy-9-methyl-1-oxa-spiro[4,5]-decane (4h). As for **4b**, but with (+)-**1h** (0.049 g, 0.25 mmol), I_2 (0.013 g, 0.050 mmol), HTIB (0.294 g, 0.750 mmol), MeOH (1 mL), and 26 h. Purification (0−5% Et_2O in CH_2Cl_2) gave **4h** (0.032 g, 57%) as a colorless oil and as a 1:1 mixture of diastereomers. IR (KBr): 1063, 1090, 1114, 1139, 1365, 1456, 2867, 2927, 2951 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ major 0.81−0.93 (m, 11H), 1.02−1.12 (m, 1H), 1.38−1.58 (m, 3H), 1.61−1.77 (m, 3H), 1.85−1.99 (m, 1H), 2.06−2.31 (m, 1H), 3.31 (s, 3H), 3.66−4.03 (m, 3H); δ minor 0.81−0.93 (m, 11H), 1.02−1.12 (m, 1H), 1.38−1.58 (m, 3H), 1.61−1.77 (m, 3H), 1.85−1.99 (m, 1H), 2.06−2.31 (m, 1H), 3.28 (s, 3H), 3.66−4.03 (m, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ major 18.1, 21.8, 22.3, 23.9, 26.4, 28.8, 35.0, 41.6, 48.5, 49.2, 57.2, 71.0, 81.3, 85.8; δ minor 18.1, 22.1, 22.3, 23.9, 25.9, 28.7, 35.1, 41.5, 47.6, 48.6, 56.6, 70.4, 81.4, 86.0. LRMS m/z (%): major 226 ($M^{\bullet+}$, 7), 211 (5), 195 (5), 183 (4), 169 (10), 155 (11), 141 (100), 123 (7), 109 (47), 95 (8); minor 226 ($M^{\bullet+}$, 7), 211 (6), 195 (5), 183 (3), 169 (12), 155 (15), 141 (100), 123 (8), 109 (46), 95 (8). HRMS [ESI(+)] calcd for $[C_{14}H_{26}O_2 + Na]^+$ 249.18305, found 249.18250.

(±)-4-Methoxydecahydro-2′*H*,3*H*-spiro[furan-2,1′-naphthalene] (4i). As for **4b**, but with **1i** (0.049 g, 0.250 mmol), I_2 (0.013 g, 0.050 mmol), HTIB (0.294 g, 0.750 mmol), MeOH (1 mL), and 45 h. Purification (10−20% Et_2O in hexane) gave **4i** (0.028 g, 50%) as a colorless oil and as a 2:1 mixture of diastereomers. IR (film): 1066, 1097, 1122, 1447, 2850, 2927 cm^{-1}. ^{1}H NMR (200 MHz, $CDCl_3$): δ major 0.89−0.97 (m, 4H), 1.17−1.25 (m, 6H), 1.51−1.81 (m, 6H), 1.89−2.25 (m, 2H), 3.30 (s, 3H), 3.74−3.95 (m, 3H); δ minor 0.89−0.97 (m, 4H), 1.17−1.25 (m, 6H), 1.51−1.81 (m, 6H), 1.89−2.25 (m, 2H), 3.28 (s, 3H), 3.74−3.95 (m, 3H). ^{13}C NMR (MHz, $CDCl_3$): δ major 22.1, 25.6, 26.3, 26.9, 33.9, 34.8, 38.3, 39.1, 40.9, 50.2, 57.0, 71.9, 81.4, 83.8; δ minor 22.0, 25.4, 26.4, 26.9, 34.0, 35.0, 38.0, 38.6, 40.8, 49.4, 56.7, 71.1, 81.4, 83.9. LRMS m/z (%): 224 ($M^{\bullet+}$, 8), 181 (50), 127 (41), 114 (22), 95 (52), 79 (41). HRMS [ESI(+)] calcd for $[C_{14}H_{24}O_2 + H]^+$ 225.1849, found 225.1848.

(±)-4-Methoxy-2-methyl-2-phenyltetrahydrofuran (4j). As for **4b**, but with **1j** (0.162 g, 1.00 mmol), I_2 (0.051 g, 0.20 mmol), HTIB (1.18 g, 3.00 mmol), MeOH (4 mL), and 4 days. Purification (5−10% THF in hexane) gave **4j** (0.048 g, 25% and 0.035 g, 18%) as two diastereomers. Major: IR (film): 703, 765, 1032, 1094, 1122, 1446, 1492, 2825, 2886, 2932, 2977, 3026, 3060, 3082. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.59 (s, 3H), 2.16−2.21 (m, 1H), 2.46 (dd, J = 6.5, 13.2 Hz, 1H), 3.31 (s, 3H), 3.88−3.98 (m, 2H), 4.01−4.04 (m, 1H), 7.18−7.25 (m, 1H), 7.29−7.34 (m, 2H), 7.37−7.40 (m, 2H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 30.5, 45.4, 56.8, 71.6, 82.0, 84.3, 124.5, 126.5, 128.2, 147.8. LRMS m/z (%): 177 (100), 145 (38), 115 (20), 105 (48), 91 (20). HRMS [ESI(+)] calcd for $[C_{12}H_{16}O_2 + H]^+$ 193.1229, found 193.1225. Minor: IR (film): 701, 763, 1082, 1113, 1447, 1492, 2828, 2856, 2926, 2961, 3026, 3060, 3088. ^{1}H (300 MHz, $CDCl_3$): δ 1.50 (s, 3H), 2.23−2.38 (m, 2H), 3.18 (s, 3H), 3.84−3.90 (m, 1H), 4.10−4.18 (m, 2H), 7.18−7.25 (m, 1H), 7.29−7.34 (m, 2H), 7.39−7.43 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 30.1, 45.2, 56.7, 71.7, 81.8, 84.1, 124.6, 126.3, 128.1, 147.6. LRMS m/z (%): 177 (100), 145 (58), 115 (35), 105 (77), 91 (41). HRMS [ESI(+)] calcd for $[C_{12}H_{16}O_2 + Na]^+$ 215.1048, found 215.1046.

(2*S*,4′*R* or 4′*S*)-4′-(Iodomethyl)-1,7,7-trimethylspiro[bicyclo-[2.2.1]heptane-2,2′-oxetane] (5k). As for **4b**, but with (+)-**1k** (0.049 g, 0.25 mmol), I_2 (0.013 g, 0.050 mmol), HTIB (0.196 g, 0.500 mmol), MeOH (1.0 mL), and 16 h. Purification (5% EtOAc in hexanes) gave **5k** (0.026 g, 33%) as a colorless oil and a 3:2 mixture of diastereomers. IR (film): 786, 1008, 1387, 1427, 1454, 2933, 2962, 2993 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ major 0.94 (s, 3H), 1.00 (s, 3H), 1.05 (s, 4H), 1.27−1.33 (m, 1H), 1.36−1.50 (m, 2H), 1.59−1.62 (m, 1H), 1.70−1.71 (m, 1H), 1.76 (dd, J = 3.7, 13.3 Hz, 1H), 1.94 (ddd, J = 2.6, 4.2, 9.6 Hz, 1H), 2.09 (dd, J = 9.2, 13.3 Hz, 1H), 3.19 (dd, J = 8.5, 9.4 Hz, 1H), 3.33 (dd, J = 5.0, 9.4 Hz, 1H), 4,21−4,31 (m, 1H); δ minor 0.93 (s, 3H), 1.00 (s, 3H), 1.03 and 1.05 (s, 4H), 1.27−1.33 (m, 1H), 1.36−1.50 (m, 2H), 1.59−1.62 (m, 2H), 1.68−1.69 (m, 1H), 2.04 (ddd, J = 1.7, 2.6, 9.6 Hz, 1H), 2.19 (dd, J = 6.0, 12.6 Hz, 1H), 3.01 (dd, J = 9.4, 9.4 Hz, 1H), 3.37 (dd, J = 4.3, 9.4 Hz, 1H), 4.21−4.31 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ major 11.3, 16.3, 22.9, 23.5, 24.7, 26.4, 34.6, 39.0, 44.9, 50.3, 58.7, 78.3, 93.4; δ minor 11.9, 21.0, 23.0, 23.5, 24.7, 25.9, 36.6, 40.9, 46.3, 49.2, 60.0, 79.0, 92.6. HRMS [ESI(+)] calcd for $[C_{13}H_{21}IO + H]^+$ 321.07098, found 321.07127.

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

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