Intramolecular Ring-Opening Reactions of 1-(2-Methoxyphenyl)-6-oxabicyclo[3.2.0]heptanes: Spirocyclic Dihydrobenzofurans from Fused Bicyclic Oxetanes

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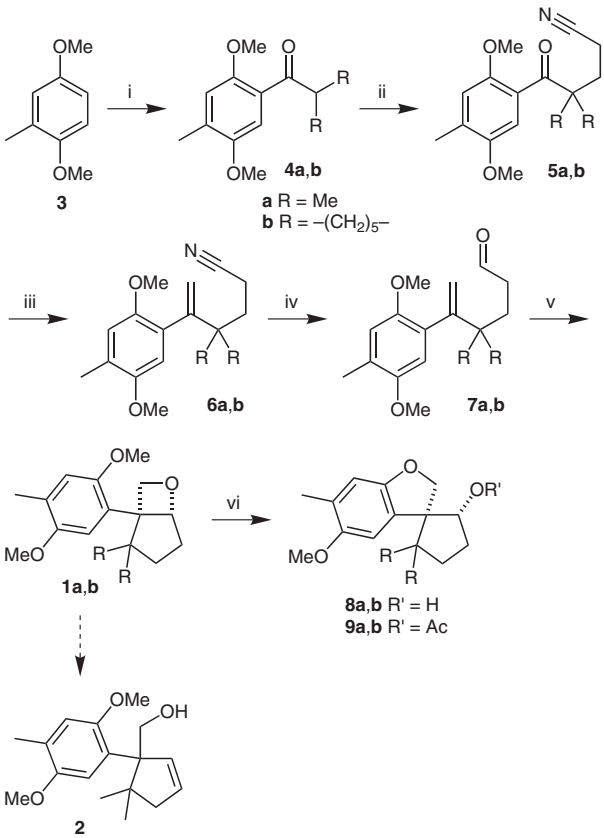
Abstract: Treatment of fused oxetanes with Et_2AlCl, TMSCl, acetyl chloride, or ethereal hydrochloric acid leads to the formation of spirocyclic dihydrobenzofurans through intramolecular attack of an oxygen atom of a proximal phenolic methyl ether.

Key words: cyclizations, heterocycles, Lewis acids, neighboring-group effects, spiro compounds

The regio- and stereoselective ring opening of oxetanes has been extensively utilized in organic synthesis as a route to functionalized alcohols.[1] Intramolecular attack on oxetanes has been less frequently studied than the intermolecular case, although examples of opening with carbon,[2] nitrogen,[3,4] sulfur,[3] and oxygen[3,5–11] nucleophiles have been reported. Attack by oxygen nucleophiles is known under both acidic and basic conditions. Masaki reported the Lewis acid catalyzed rearrangement of monosubstituted oxetanes to give ring-expanded cyclic ethers accompanied by transfer of ethereal benzylic and allylic groups.[8] Intramolecular attack of phenoxide, generated in situ by methyllithium-mediated deprotection of a pivaloyl ester, on a disubstituted oxetane, led to the formation of a substituted dihydrobenzofuran.[3]

As part of our studies on the application of an intramolecular Paternò–Büchi photocyclization–oxetane fragmentation sequence to the synthesis of herbertane and cuparene sesquiterpenes,[11] we required a means of converting oxetane **1a** into the homoallylic alcohol **2**. Oxetane **1a** was readily prepared in five steps from commercially available 2,5-dimethoxytoluene **3** (Scheme 1) according to a general route we have previously developed.[11,12] Attempted ring opening of **1a** using the Yamamoto protocol (diethylaluminium chloride and *N*-methylanilide in refluxing benzene)[13] failed to provide any of the expected homoallylic alcohol **2**, but instead led to recovery of starting material. However, we fortuitously discovered that omission of *N*-methylanilide led to the formation of a new compound, the spirobenzofuran **8a**, in reasonable yield at room temperature (Table 1, entry 1).

Further screening of reagents showed that even simpler activators could be used in place of the metal Lewis acid: treatment of oxetane **1a** with trimethylsilyl chloride, acetyl chloride or ethereal hydrochloric acid all resulted in the formation of a spirobenzofuran in good yield (Table 1, entries 2–4). In the case of trimethylsilyl chloride, the initial product was the trimethylsilyl ether (observable by TLC), which subsequently hydrolyzed to alcohol **8a**[14] upon aqueous workup. Use of acetyl chloride directly led



Scheme 1 *Reagents and conditions:* i) for **4a**: $Me_2CHCOCl$, $AlCl_3$, CH_2Cl_2, 0 °C to r.t., 2 h, 98%; for **4b**: $C_6H_{11}COCl$, $AlCl_3$, $ClCH_2CH_2Cl$, r.t., 3 h, 70%; ii) acrylonitrile, tetrabutylammonium hydroxide (1 M, MeOH), 1,4-dioxane, 35 °C; for **5a**: 72 h, 82%; for **5b**: 48 h, 20% (+70% RSM); iii) Ph_3PMeBr, KO*t*-Bu, toluene, 60 °C; for **6a**: 17 h, 94%; for **6b**: 48 h, 67%; iv) DIBAL-H, CH_2Cl_2, –78 °C to 0 °C, 3 h; for **7a**: 85%; for **7b**: 91%; v) hexane, medium-pressure (125 W) mercury arc lamp, Pyrex immersion well photoreactor, r.t.; for **1a**: 0.01 M, 18 h, 61%; for **1b**: 0.005 M, 4 h, 53%; vi) Table 1.

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to the corresponding ester **9a**[15] (entry 4). Formation of 1,3-chlorohydrins, typical products in the intermolecular opening of oxetanes with acid derivatives, was not observed under any of these conditions.

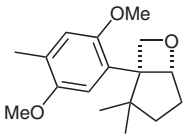
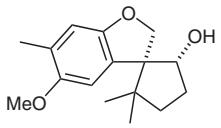
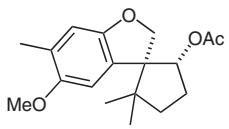
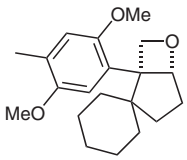
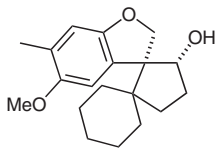
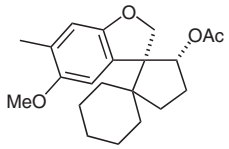
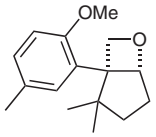
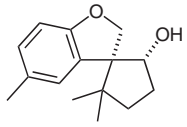
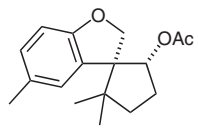
We have used this methodology to rapidly assemble an unusual bis-spirocyclic ring system. Oxetane **1b**, containing a cyclohexane ring in place of the geminal dimethyl group in **1a**, was prepared in a manner analogous to that of **1a** (Scheme 1). Treatment of **1b** with ethereal hydrochloric acid gave alcohol **8b** (Table 1, entry 5), whereas acetyl chloride gave rise to the acetate **9b** (entry 6).

Ring opening of oxetane **10**,[11] containing just one methoxy group on the aromatic ring, was also investigated. Reactions were slower than with the dimethoxy ethers **1a** and **1b**. Under acidic conditions, 34% of alcohol **11** was obtained, along with 52% recovered oxetane **10** after 24 hours at room temperature (Table 1, entry 7). A reasonable yield of acetate **12** was obtained using acetyl chloride activation after 48 hours (entry 8).

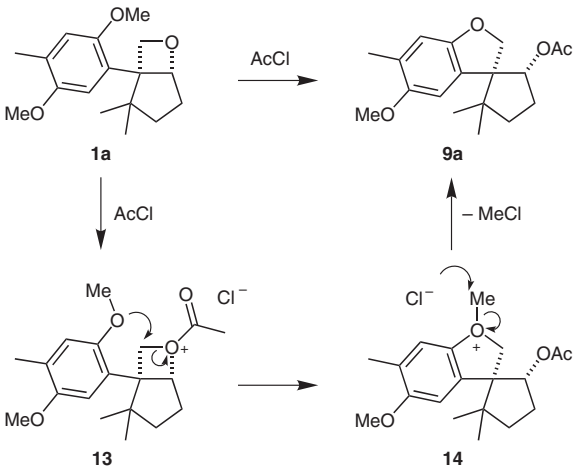
A plausible mechanism for these transformations is shown in Scheme 2, exemplified for the reaction of oxetane **1a** with acetyl chloride. Activation of the Lewis basic oxetane oxygen is followed by intramolecular attack by the neighboring phenolic ether on **13** to cleave the strained heterocycle. Loss of chloromethane from **14** through a second nucleophilic displacement leads to the spirobenzofuran **9a**.

We have also evaluated neighboring-group participation in the ring opening of the isomeric [2.2.1]oxabicyclic ether **15**, prepared from oxetane **1a** in two steps (Scheme 3). Although oxetane **1a** proved inert to the Yamamoto conditions[13] and to NaH in DMA at 100–

Table 1 Formation of Spirobenzofurans from Oxetanes

Entry	Oxetane	Conditions	Spirobenzofuran	Yield (%)
1	 **1a**	Et_2AlCl (10 equiv), toluene, 0 °C to r.t., 1 h	 **8a**	59
2	**1a**	TMSCl (10 equiv), DCE, r.t., 18 h	**8a**	76
3	**1a**	HCl (10 equiv), Et_2O, 0–5 °C, 18 h	**8a**	78
4	**1a**	AcCl (10 equiv), DCE, r.t., 18 h	 **9a**	81
5	 **1b**	HCl (10 equiv), Et_2O, 0 °C to r.t., 18 h	 **8b**	71
6	**1b**	AcCl (10 equiv), DCE, r.t., 5 h	 **9b**	61
7	 **10**	HCl (10 equiv), Et_2O, 0 °C to r.t., 24 h	 **11**	34[a]
8	**10**	AcCl (10 equiv), DCE, r.t., 48 h	 **12**	65

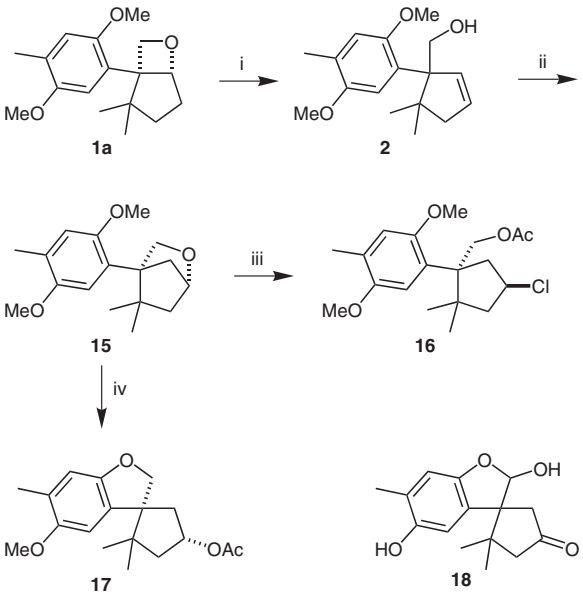
[a] Starting material (52%) was recovered.



Scheme 2

140 °C,[16] ring opening to homoallylic alcohol **2** was accomplished by treatment of **1a** with an excess of butyllithium, diisopropylamine, and potassium *tert*-butoxide in refluxing THF.[17] Treatment of alkene **2** with mercuric acetate followed by reduction of the intermediate organomercurial resulted in formation of the [2.2.1]oxabicyclic ether **15** through a formal 5-*endo*-trig ring closure.[18] Subjecting **15** to acetyl chloride did not result in spirobenzofuran formation, but instead to the formation of chloroacetate **16** in low yield.[19] However, when **15** was treated with ZnI_2 and acetic anhydride, known conditions for the cleavage of tetrahydrofurans,[20] the spirocyclic ether **17** was produced in good yield.

A comparison of the structure of **17** with that of spirobenzofuran **9a** shows that regioisomeric acetates can be prepared from the same starting oxetane **1a** in one or three steps respectively. Interestingly, **17** contains the core structure of spirobenzofuran **18**, a bioactive fungal metabolite isolated from *Acremonium* sp. HKI 0230,[21] which has recently been synthesized for the first time.[22]



Scheme 3 *Reagents and conditions*: i) KO*t*-Bu (4 equiv), BuLi (3.8 equiv), diisopropylamine (4 equiv), hexane, reflux, 24 h, 68%; (ii) a) $Hg(OAc)_2$ (1.25 equiv), THF–H_2O (1:1), r.t., 16 h; (b) 3 M NaOH, 0.5 M $NaBH_4$ in 3 M NaOH, 88%; iii) AcCl, Et_2O, 0 °C, r.t., 18 h, 18%; iv) ZnI_2 (1.5 equiv), Ac_2O, r.t., 20 h, 78%.

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References and Notes

(1) Linderman, R. J. In *Comprehensive Heterocyclic Chemistry II*, Vol. 1B; Katritzky, A. R.; Rees, C. W.; Scriven, E. F. V.; Padwa, A., Eds.; Elsevier: Oxford, **1996**.
(2) Yamaguchi, M.; Hirao, I. *Tetrahedron Lett.* **1984**, *25*, 4549.
(3) (a) Bach, T.; Kather, K. *J. Org. Chem.* **1996**, *61*, 7642. (b) Bach, T.; Kather, K.; Krämer, O. *J. Org. Chem.* **1998**, *63*, 1910.
(4) (a) Ng, F. W.; Lin, H.; Tan, Q.; Danishefsky, S. J. *Tetrahedron Lett.* **2002**, *43*, 545. (b) Ng, F. W.; Lin, H.; Danishefsky, S. J. *J. Am. Chem. Soc.* **2002**, *124*, 9812.
(5) Corey, E. J.; Raju, N. *Tetrahedron Lett.* **1983**, *24*, 5571.
(6) Capek, K.; Vydra, T.; Sedmera, P. *Carbohydr. Res.* **1987**, *168*, c1.
(7) Khan, N.; Morris, T. H.; Smith, E. H.; Walsh, R. *J. Chem. Soc., Perkin Trans. 1* **1991**, 865.
(8) Itoh, A.; Hirose, Y.; Kashiwagi, H.; Masaki, Y. *Heterocycles* **1994**, *38*, 2165.
(9) In taxoids, the close proximity of the C-2 hydroxy group with the oxetane ring allows for a particularly facile intramolecular S_N2 displacement at C-20 leading to the formation of tetrahydrofurans: (a) Farina, V.; Huang, S. *Tetrahedron Lett.* **1992**, *33*, 3979. (b) Wahl, A.; Guéritte-Voegelein, F.; Guénard, D.; Le Goff, M.-T.; Potier, P. *Tetrahedron* **1992**, *48*, 6965. (c) Klein, L. L. *Tetrahedron Lett.* **1993**, *34*, 2047. (d) Nicolaou, K. C.; Renaud, J.; Nantermet, P. G.; Couladouros, E. A.; Guy, R. K.; Wrasidlo, W. *J. Am. Chem. Soc.* **1995**, *117*, 2409. (e) Danishefsky, S. J.; Masters, J. J.; Young, W. B.; Link, J. T.; Snyder, L. B.; Magee, T. V.; Jung, D. K.; Isaacs, R. C. A.; Bornmann, W. G.; Alaimo, C. A.; Coburn, C. A.; Di Grandi, M. J. *J. Am. Chem. Soc.* **1996**, *118*, 2843. (f) Ojima, I.; Lin, S.; Inoue, T.; Miller, M. L.; Borella, C. P.; Geng, X.; Walsh, J. T. *J. Am. Chem. Soc.* **2000**, *122*, 5343.
(10) Bach, T.; Schröder, J. *J. Org. Chem.* **1999**, *64*, 1265.
(11) Boxall, R. J.; Ferris, L.; Grainger, R. S. *Synlett* **2004**, 2379.
(12) Grainger, R. S.; Patel, A. *Chem. Commun.* **2003**, 1072.
(13) Kitagawa, Y.; Itoh, A.; Hashimoto, S.; Yamamoto, H.; Nozaki, H. *J. Am. Chem. Soc.* **1977**, *99*, 3864.
(14) **Typical Experimental for Oxetane Ring-Opening Reaction with HCl**
To a solution of oxetane **1a** (50 mg, 0.18 mmol) in Et_2O (5 mL) at 0 °C HCl (1 M in Et_2O, 1.80 mL, 1.80 mmol) was added over a period of 10 min. The resulting solution was stirred for 18 h at r.t. The resulting mixture was poured into H_2O (10 mL) and the aqueous layer was extracted with Et_2O (2 × 10 mL). The combined organic phases were washed with brine (10 mL), dried over $MgSO_4$, filtered and concentrated in vacuo. The crude product was purified via column chromatography (hexane–EtOAc, 8:2) to furnish spirocycle **8a** as a colorless oil (37 mg, 78%). R_f = 0.2 (hexane–EtOAc, 8:2); mp 88–90 °C. IR (neat): ν_{max} = 3445, 2945, 2865, 1651, 1497, 1466, 1199 cm^{-1}. ^1H NMR (360

MHz, $CDCl_3$): δ = 6.65 (1 H, s, CC*H*COCH$_3$), 6.58 (1 H, s, CH$_2$OCC*H*CCH$_3$), 5.07 (1 H, dd, *J* = 6.8, 1.8 Hz, C*H*OH), 3.93 (1 H, d, *J* = 11.0 Hz, COCH$_2$C), 3.79 (3 H, s, ArOCH$_3$), 3.65 (1 H, d, *J* = 11.0 Hz, COCH$_2$C), 2.19 (3 H, s, ArCH$_3$), 2.16–2.11 (1 H, m, HOCHC*H*$_2$CH$_2$), 1.97–1.94 (1 H, m, HOCHC*H*$_2$CH$_2$), 1.61–1.50 (1 H, m, HOCHCH$_2$C*H*$_2$), 1.49–1.44 (1 H, m, HOCHCH$_2$C*H*$_2$), 1.26 (1 H, br, OH), 1.07 [3 H, s, C(CH$_3$)$_2$], 1.03 [3 H, s, C(CH$_3$)$_2$]. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 17.0 (q), 24.6 (q), 26.7 (q), 32.2 (t), 40.9 (t), 44.9 (s), 56.9 (q), 64.9 (s), 65.2 (t), 92.8 (d), 108.6 (d), 111.7 (d), 125.3 (s), 128.2 (s), 152.1 (s), 156.1 (s). ESI-HRMS: *m/z* calcd for $C_{16}H_{22}O_3Na$: 285.1461; found: 285.1457; LRMS (EI): *m/z* (%) = 262 (100) [M$^+$], 231 (5), 205 (33), 192 (6), 175 (33), 163 (9).

(15) **Typical Experimental Procedure for Oxetane Ring-Opening Reaction with AcCl**
To a solution of oxetane **1a** (50 mg, 0.18 mmol) in DCE (10 mL) at r.t., AcCl (0.13 mL, 1.80 mmol) was added. The resulting solution was stirred overnight at r.t. poured into H_2O (10 mL) and the aqueous layer was extracted with CH_2Cl_2 (2 × 10 mL). The combined organic phases were dried over $MgSO_4$, filtered, and reduced in vacuo. The crude product was purified via column chromatography (hexane–EtOAc, 9:1) to furnish spirocycle **9a** as a colorless oil (45 mg, 81%). R_f = 0.2 (hexane–EtOAc, 9:1). IR (neat): ν_{max} = 2950, 2869, 2252, 2105, 1739, 1651, 1490, 1464, 1223, 1047 cm^{-1}. ^{1}H NMR (360 MHz, $CDCl_3$): δ = 6.66 (1 H, s, CC*H*COCH$_3$), 6.54 (1 H, s, CH$_2$OCC*H*CCH$_3$), 4.96 (1 H, dd, *J* = 6.8, 1.6 Hz, C*H*OCOCH$_3$), 4.45 (1 H, d, *J* = 11.1 Hz, COCH$_2$C), 4.16 (1 H, d, *J* = 11.2 Hz, COCH$_2$C), 3.77 (3 H, s, ArOCH$_3$), 2.18 (3 H, s, ArCH$_3$), 2.15–2.12 (1 H, m, COCHC*H*$_2$CH$_2$), 1.97 (3 H, s, OCOCH$_3$), 1.99–1.91 (1 H, m, COCHC*H*$_2$CH$_2$), 1.63–1.55 (1 H, m, COCHCH$_2$C*H*$_2$), 1.52–1.48 (1 H, m, COCHCH$_2$C*H*$_2$), 1.10 [3 H, s, C(CH$_3$)$_2$], 1.06 [3 H, s, C(CH$_3$)$_2$]. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 16.5 (q), 20.9 (q), 24.6 (q), 26.4 (q), 31.9 (t), 39.6 (t), 44.9 (s), 56.4 (q), 61.7 (s), 67.1 (t), 92.3 (d), 109.0 (d), 111.2 (d), 125.9 (s), 127.3 (s), 151.4 (s), 154.8 (s), 171.0 (s). ESI-HRMS: *m/z* calcd for $C_{18}H_{24}O_4Na$: 327.1567; found: 327.1562. LRMS (EI): *m/z* (%) = 304 (100) [M$^+$], 262 (21), 175 (66), 160 (8), 115 (8), 91 (7), 69 (5), 43 (16).

(16) Joshi, B. V.; Rao, T. S.; Reese, C. B. *J. Chem. Soc., Perkin Trans. 1* **1992**, 2537.

(17) Thurner, A.; Faigl, F.; Tőke, L.; Mordini, A.; Valacchi, M.; Reginato, G.; Czira, T. *Tetrahedron* **2001**, *57*, 8173.

(18) (a) Kočovský, P.; Pour, M. *J. Org. Chem.* **1990**, *55*, 5580. (b) Polt, R.; Wijayaratne, T. *Tetrahedron Lett.* **1991**, *32*, 4831.

(19) Ring opening by chloride on activated **15** can lead to two possible regioisomeric chloroacetates. The stucture of **16** was confirmed by a long-range COSY experiment, and configuration at the chloro-substituted stereocenter was possible through NOESY correlation. The stereochemical outcome of this reaction suggests it also likely proceeds via an S_N2-type ring opening of the activated ether with chloride nucleophile, where the regiochemical outcome is presumably a result of the preferred attack by chloride at a secondary carbon over a primary neopentyl-like carbon. For an analogous example in oxetane ring opening using HCl, see: Ceccherelli, P.; Curini, M.; Marcotullio, M. C. *J. Chem. Soc., Perkin Trans. 1* **1985**, 2173.

(20) (a) Benedetti, M. O. V.; Monteagudo, E. S.; Burton, G. *J. Chem. Res., Synop.* **1990**, 248. (b) Hernández, R.; Velázquez, S. M.; Suárez, E. *J. Org. Chem.* **1994**, *59*, 6395. (c) Abad, A.; Agulló, C.; Cuñat, A. C.; García, A. B.; Giménez-Saiz, C. *Tetrahedron* **2003**, *59*, 9523.

(21) Kleinwächter, P.; Schlegel, B.; Dörfelt, H.; Gräfe, U. *J. Antibiot.* **2001**, *54*, 526.

(22) Srikrishna, A.; Lakshmi, B. V. *Tetrahedron Lett.* **2005**, *46*, 7029.