A Rapid Total Synthesis of (±)-Sylvone

Christopher G. Nasveschuk, Tomislav Rovis*

Department of Chemistry, Colorado State University, Fort Collins, CO 80523, USA
Fax +1(970)4911801; E-mail: rovis@lamar.colostate.edu.

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Abstract: We report a convergent and diastereoselective synthesis of (±)-sylvone that utilizes a diastereoselective [1,3] ring contraction.

Key words: ring contraction, [1,3] rearrangement, 1,3-dioxepin, tetrahydrofuran, sylvone

Furofuran lignans are a large and diverse class of molecules that possess a tetrahydrofuran core and ornamental aromatic substitution. Typically isolated from plant material, many of which are used in indigenous and traditional herbal medicines, furofurans display broad biological activity.[1] New lignans continue to be isolated and have thus compelled the community to develop new synthetic methodology that provides access to the variety of different substitution patterns possessed by these molecules.[1,2] Of currently existing strategies, there are few that provide direct and efficient construction of 2,3,4-trisubstituted tetrahydrofurans.[3] Perhaps the most elegant of these approaches was reported by Marsden and co-workers in which substituted tetrahydrofurans may be constructed by condensation of an aldehyde and a [1,2]oxasilepine.[4] As part of a program to study [1,3] rearrangements,[5] we have developed a complementary approach to the 2,3,4-trisubstituted tetrahydrofuran framework via a diastereoselective [1,3] ring contraction of 1,3-dioxepins.[6] Herein we describe the successful implementation of this strategy in the synthesis of furofuran lignan (±)-sylvone (**1**) (Figure 1).

Sylvone (**1**) is a furofuran lignan isolated by Banerji and co-workers from the petrol extracts of seeds derived from *piper sylvaticum*.[7] Although the bioactivity profile of **1** is not known, other members of its class display a range of activity including antitumor, antimitotic, and antiviral characteristics.[8] Interestingly, of this subclass of furofuran lignans, only sesaminone has been synthesized. Gordon and co-workers used a diastereoselective *syn* aldol to set the relative stereochemistry of the tetrahydrofuran core while Yoda and co-workers employed a diastereoselective Grignard aldehyde alkylation.[9] We envisioned the formation of the 2,3,4-trisubstituted tetrahydrofuran core of sylvone by a ring contraction of a 1,3-dioxepin. This strategy revolves around the use of *cis*-1,4-butene diol as a lynchpin (Figure 1). The diol is functionalized with an aldehyde to provide a symmetrical 1,3-dioxepin. The olefin is subsequently desymmetrized by a Heck reaction, which simultaneously adds a necessary aryl substituent and activates the system towards [1,3] rearrangement (Scheme 1).

The synthetic sequence commences with condensation of *cis*-1,4-butenediol and veratraldehyde. An intermolecular Heck reaction between **5**[10] and 1,1-disubstituted alkene **6**[11] proceeds in excellent diastereoselectivity and moderate yield (Scheme 2). It was found that increasing the catalyst loading or extending the reaction time does not improve the yield.[12]

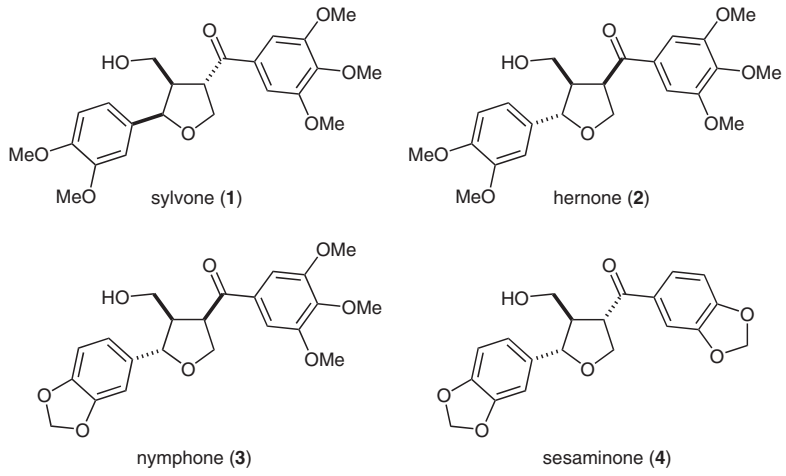

Figure 1 Furofuran lignans

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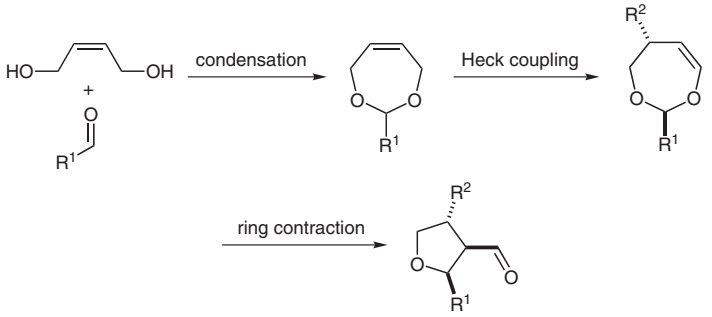
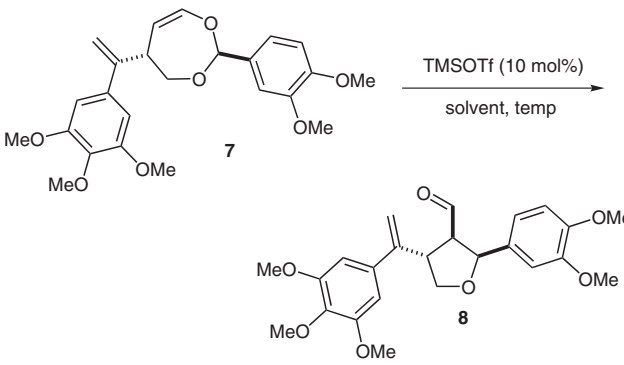


Scheme 1 Strategy

Ring contraction of key dioxepin **7**[13] under our previously reported conditions leads to complex mixtures of unidentifiable products (Table 1, entry 1). It was hypothesized that exposure to aqueous acid during workup facilitated product decomposition. This pitfall was overcome by low temperature quench of the Lewis acid with Et_3N followed by an aqueous $NaHCO_3$ workup. Unfortunately, the TMSOTf–MeCN conditions produce the desired tetrahydrofuran with modest diastereomeric ratio. Only two of the four possible diastereomers are formed, where the major diastereomer is the 2,3-*cis*/3,4-*trans* product and the minor diastereomer contains the 2,3-*trans*/3,4-*cis* relative configuration (entry 2). Diastereoselectivity may be restored by changing the solvent to EtCN, which allows access to lower reaction temperatures (entry 3).[14]

The remainder of the synthesis proceeded without incident (Scheme 3). Reduction of the aldehyde with $NaBH_4$ is followed by dihydroxylation of the 1,1-disubstituted olefin. Finally, oxidative cleavage with $NaIO_4$ produces (±)-sylvone[15] in 85% from **7**. Due to the acid-sensitive nature of tetrahydrofuran **8** and the complex diastereomeric mixture derived from facially unselective dihydroxylation, this four-reaction sequence was performed without intermediate purification. Upon workup, (±)-sylvone was isolated as a white solid whose physical data matched the reported literature values.[7] The synthesis was completed in 33% overall yield for six linear steps from commercially available materials.

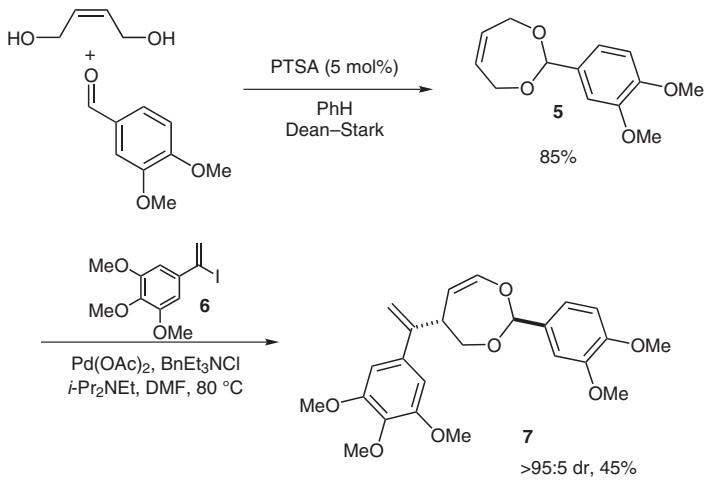
Table 1 Optimization of Ring Contraction



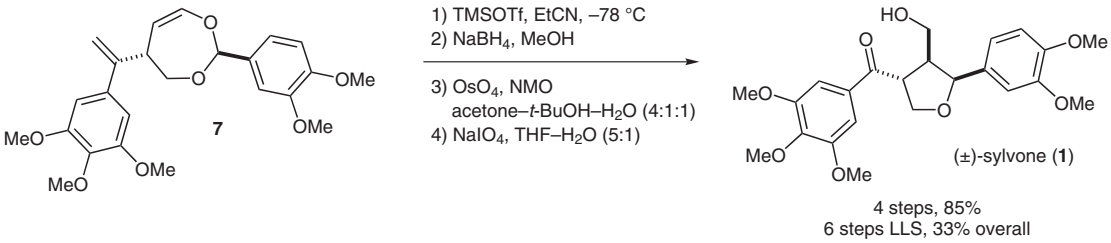
Entry	Solvent	Temp (°C)	dr
1	MeCN	–40	ND[a]
2	MeCN	–40	78:22[b]
3	EtCN	–78	90:10[b]

[a] The reaction was quenched with aq NH_4Cl; ND = not determined.
[b] The reaction was quenched with Et_3N.

In conclusion, we have developed a rapid total synthesis of (±)-sylvone. The salient features of this sequence are the sequential installation of each aryl group followed by a diastereoselective [1,3] ring contraction. This allows us to systematically vary the substitution around the furofu-



Scheme 2 Synthesis of key 1,3-dioxepin



Scheme 3 Completion of (±)-sylvone

ran core as a route to any member of this family of natural products.

Acknowledgment

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References and Notes

(1) For reviews concerning lignans, see: (a) MacRae, W. D.; Towers, G. H. N. *Phytochemistry* **1984**, *23*, 1207. (b) Whiting, D. A. *Nat. Prod. Rep.* **1987**, *4*, 499. (c) Ward, R. S. *Nat. Prod. Rep.* **1993**, *10*, 1. (d) Ward, R. S. *Nat. Prod. Rep.* **1995**, *12*, 183. (e) Ward, R. S. *Nat. Prod. Rep.* **1997**, *14*, 43. (f) Ward, R. S. *Nat. Prod. Rep.* **1997**, *16*, 75.

(2) For reviews on the strategies of oxacycle synthesis, see: (a) Faul, M. M.; Huff, B. E. *Chem. Rev.* **2000**, *100*, 2407. (b) Elliott, M. C. *J. Chem. Soc., Perkin Trans. 1* **2002**, 2301.

(3) For methods resulting in a total synthesis of a furofuran lignan, see: (a) Takano, S.; Samizu, K.; Ogasawara, K. *Synlett* **1993**, 785. (b) Akindele, T.; Marsden, S. P.; Cumming, J. G. *Org. Lett.* **2005**, *7*, 3685. (c) Wardrop, D. J.; Fritz, J. *Org. Lett.* **2006**, *8*, 3659. (d) Review: Brown, R.; Swain, N. A. *Synthesis* **2004**, 811.

(4) (a) Cassidy, J. H.; Marsden, S. P.; Stemp, G. *Synlett* **1997**, 1411. (b) Miles, S. M.; Marsden, S. P.; Leatherbarrow, R. J.; Coates, W. J. *J. Org. Chem.* **2004**, *69*, 6874.

(5) (a) Zhang, Y.; Reynolds, N. T.; Manju, K.; Rovis, T. *J. Am. Chem. Soc.* **2002**, *124*, 9720. (b) Zhang, Y.; Rovis, T. *Tetrahedron Lett.* **2003**, *59*, 8979. (c) Nasveschuk, C. G.; Rovis, T. *Org. Lett.* **2005**, *7*, 2173. (d) Nasveschuk, C. G.; Rovis, T. *Angew. Chem. Int. Ed.* **2005**, *44*, 3264. (e) Frein, J. D.; Rovis, T. *Tetrahedron* **2006**, *62*, 4573.

(6) Nasveschuk, C. G.; Jui, N. T.; Rovis, T. *Chem. Commun.* **2006**, 3119.

(7) (a) Banerji, A.; Sarkar, M.; Ghosal, T.; Pal, S. C.; Shoolery, J. N. *Tetrahedron* **1984**, *40*, 5047. (b) Banerji, A.; Basu, S. *J. Indian Chem. Soc.* **1992**, *69*, 321.

(8) For reports that discuss the bioactivity of lignans, see: (a) Chen, I.-S.; Chen, J.-J.; Duh, C.-Y.; Tsai, I.-L. *Phytochemistry* **1997**, *45*, 991. (b) Parmar, V. S.; Jain, S. C.; Bisht, K. S.; Jain, R.; Taneja, P.; Jha, A.; Tyagi, O. D.; Prasad, A. K.; Wengel, J.; Olsen, C. E.; Boll, P. M. *Phytochemistry* **1997**, *46*, 597.

(9) (a) Maioli, A. T.; Civiello, R. L.; Foxman, B. M.; Gordon, D. M. *J. Org. Chem.* **1997**, *62*, 7413. (b) Yoda, H.; Kimura, K.; Takabe, K. *Synlett* **2001**, 400.

(10) **2-(3,4-Dimethoxyphenyl)-4,7-dihydro[1,3]dioxepine (5)**: ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.08–7.02 (2 H, m), 6.84 (1 H, d, *J* = 8.1 Hz), 5.79 (1 H, s), 5.75 (2 H, s), 4.41–4.19 (4 H, m), 3.88 (3 H, s), 3.86 (3 H, s). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 149.2, 148.9, 131.8, 130.2, 118.9, 110.8, 109.7, 102.3, 64.7, 56.1. IR (NaCl dep. from $CHCl_3$): 2942, 2837, 1516, 1259, 1160, 777 cm^{-1}.

(11) For a procedure to prepare **6**, see: Scannell, R. T.; Stevenson, R. *J. Heterocycl. Chem.* **1980**, *17*, 1727.

(12) Vinyl iodide **6** is consumed in these reactions. Small amounts of dioxepin **5** could be re-isolated (ca. 20%).

(13) **2-(3,4-Dimethoxyphenyl)-5-[1-(3,4,5-trimethoxyphenyl)vinyl]-4,5-dihydro[1,3]dioxepine (7)**: ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.08–7.02 (2 H, m), 6.84 (1 H, d, *J* = 8.3 Hz), 6.62 (2 H, s), 6.53 (1 H, dd, *J* = 7.5, 3.0 Hz), 5.49 (1 H, s), 5.38 (1 H, s), 5.19 (1 H, s), 5.01 (1 H, d, *J* = 7.3 Hz), 4.23 (1 H, d, *J* = 11.5, 4.5 Hz), 3.94–3.82 (16 H, m), 3.38 (1 H, dd, *J* = 11.1, 11.1 Hz). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 153.3, 149.6, 149.1, 148.4, 145.3, 138.2, 136.9, 131.6, 118.7, 114.2, 113.3, 110.9, 109.0, 106.4, 103.9, 74.4, 61.1, 56.4, 56.2, 56.1, 46.9. IR (NaCl dep. from $CHCl_3$): 2937, 2836, 1645, 1411, 1128, 732 cm^{-1}. HRMS (+TOF MS): *m/z* calcd for $C_{24}H_{29}O_7$ [M + H]$^+$: 429.1908; found: 429.1893.

(14) **Procedure for the Stereoselective Ring Contraction of 7**
A flame-dried round-bottomed flask was purged with argon then charged with propionitrile (0.1 M with respect to 1,3-dioxepin) and 0.1 equiv of TMSOTf. The solution was cooled to –78 °C. A separate flame-dried round-bottomed flask was purged with argon and charged with propionitirile (0.1 M with respect to 1,3-dioxepin) and 1 equiv of **7**. The solution was then cooled to –78 °C. The solution containing **7** was transferred via cannula to the solution containing Lewis acid at an approximate rate of 1 mL/min. The solution was allowed to mix for 1 h at –78 °C. When the reaction was complete the Lewis acid was quenched with 1 equiv of Et_3N and subsequently poured into sat. aq $NaHCO_3$. The aqueous layer was extracted with Et_2O (3 ×), then the organic layer was dried with $MgSO_4$. After filtration the solvent removed in vacuo and the crude product was carried through the remainder of the synthetic steps to afford (±)-sylvone **1**.

(15) **(±)-Sylvone (1)**
^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.41 (2 H, s), 6.84 (3 H, m), 5.03, (1 H, d, *J* = 6.0 Hz), 4.43 (1 H, dd, *J* = 7.9, 7.9 Hz), 4.31 (1 H, ddd, *J* = 7.7, 5.8, 2.8 Hz), 4.24 (1 H, dd, *J* = 8.1, 5.8 Hz), 3.96–3.77 (15 H, m), 3.41 (2 H, d, *J* = 6.4 Hz), 2.89 (1 H, ddd, *J* = 6.2, 6.0, 2.8 Hz), 1.40 (1 H, br s). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 198.7, 153.3, 149.1, 148.4, 142.9, 131.5, 130.6, 117.9, 111.2, 108.9, 106.4, 81.5, 69.1, 62.1, 61.1, 56.4, 56.0, 56.0, 49.9, 48.9. IR (NaCl dep. from $CHCl_3$): 3516, 2941, 1673, 1516, 1127, 731 cm^{-1}. MS (EI$^+$): *m/z* calcd for $C_{23}H_{28}O_8$ [M + H]$^+$: 433.2; found: 433.3.