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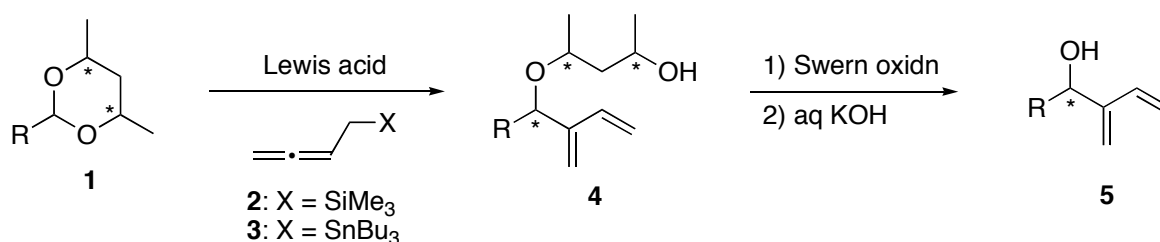
ENANTIOSELECTIVE ROUTE TO ARYL(1,3-BUTADIEN-2-YL)METHANOLS: FORMAL SYNTHESIS OF (–)-SPOROCHNOL A[†]

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Abstract – Ti(IV)-promoted reaction of the chiral acetals derived from aromatic aldehydes with 1-(tri-*n*-butyl)stannyl-2,3-butadiene followed by removal of the chiral auxiliary gave aryl(1,3-butadien-2-yl)methanols with high enantiomeric purity (>90% ee). The synthetic utility of this method was demonstrated by the formal synthesis of (–)-sporochnol A, a terpene possessing a chiral benzylic quaternary carbon center.

We have previously developed an effective method for the highly enantioselective preparation of dienol **5** via Lewis acid-promoted reaction of chiral acetal **1** with buta-2,3-dienylsilane **2**.^{1,2} In addition, we have demonstrated the synthetic utility of **5** as a chiral building block by utilizing it in the synthesis of natural products.³ However, this method could not be applied to the synthesis of the compounds having aromatic substituents **5** (R = Ar) due to the instability of **4** under the reaction conditions. We now report a highly enantioselective route to aryl(1,3-butadien-2-yl)methanols **5** (R = Ar) through butadienylation of **1** with buta-2,3-dienylstannane **3**^{4,5} using a mild mixed Ti(IV) reagent as a promoter.

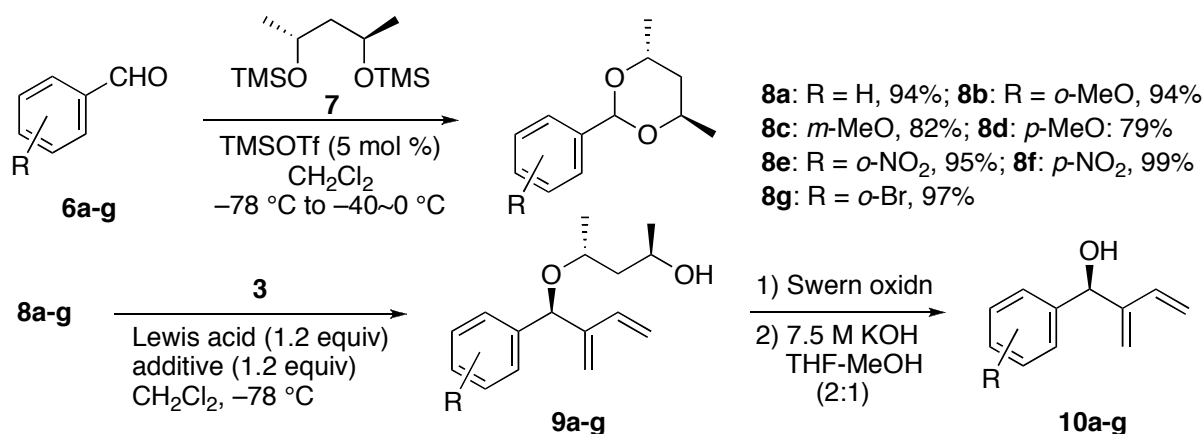


Scheme 1

[†] Dedicated to Professor Emeritus Keiichiro Fukumoto on the occasion of his 75th birthday.

We also demonstrate the utility of this methodology by the formal synthesis of (–)-sporochinol A, an enantiomer of which is a fish deterrent isolated from the marine alga *Sporchnus bolleanus*.^{6,7}

To establish a reliable method for the preparation of aryl(1,3-butadien-2-yl)methanols **5** (R = Ar) in high enantiomeric purity, we examined the dienylation of chiral acetals **8a-g**, prepared by acetalization of aldehydes **6a-g** with **7**,⁸ using BF₃·Et₂O and 3TiCl₄·Ti(O-*i*-Pr)₄ as a promoter according to the procedure⁴ previously established for the reaction of dimethyl acetals (Scheme 2, Table 1). The reactions were evaluated by HPLC analysis using a chiral column after converting **9** to **10** by Swern oxidation followed by retro-Michael reaction. The absolute configurations of **10** were determined to be *S* by ¹H NMR analysis of *R*- and *S*-MTPA esters. As can be seen from Table 1, BF₃·Et₂O did not promote the dienylation at all in the case of chiral acetals unlike the corresponding dimethyl acetals⁴ (entries 1 and 3). On the other hand, 3TiCl₄·Ti(O-*i*-Pr)₄ was found to effectively promote the dienylation of **8a** and other acetals **8f,g** having electron-withdrawing groups (entries 2, 9, and 10). However, in the case of *o*-nitrophenyl derivative **8e**, the desired product **9e** was not produced due to the extreme insolubility of



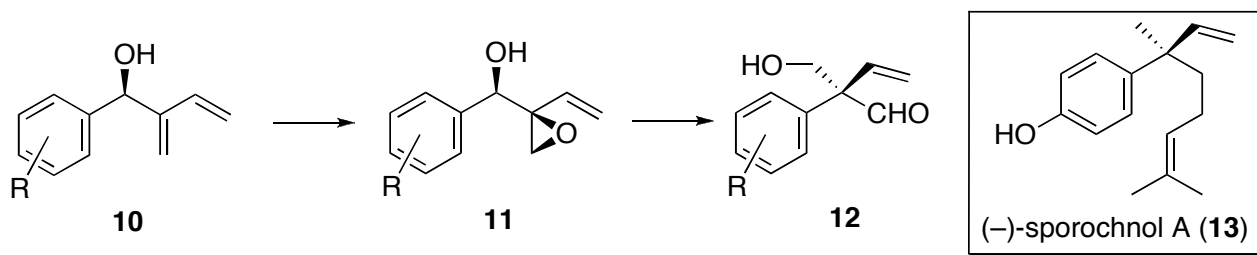
Scheme 2

Table 1. Lewis acid-promoted reaction^a of **8** with **3** and conversion of **9** to **10**.

Entry	Acetal	Lewis Acid	Additive	Time (h)	Yield of 9 (%) ^b	Yield of 10 (%) ^b	Ee % of 10 ^{c,d}
1	8a	BF ₃ ·Et ₂ O		21	0	—	—
2	8a	3TiCl ₄ ·Ti(O- <i>i</i> -Pr) ₄		12	70	89	91
3	8b	BF ₃ ·Et ₂ O		8	0	—	—
4	8b	3TiCl ₄ ·Ti(O- <i>i</i> -Pr) ₄		5	32	87	78
5	8b	3TiCl ₄ ·Ti(O- <i>i</i> -Pr) ₄	MeCN	24	76	92	90
6	8c	3TiCl ₄ ·Ti(O- <i>i</i> -Pr) ₄	MeCN	24	73	90	90
7	8d	3TiCl ₄ ·Ti(O- <i>i</i> -Pr) ₄	MeCN	24	70	91	90
8	8e	3TiCl ₄ ·Ti(O- <i>i</i> -Pr) ₄		12	0	—	—
9	8f	3TiCl ₄ ·Ti(O- <i>i</i> -Pr) ₄		24	82	93	98
10	8g	3TiCl ₄ ·Ti(O- <i>i</i> -Pr) ₄		24	81	98	91

^aThe reactions were conducted at –78 °C using **8** (1 equiv), **3** (1.5 equiv), and Lewis acid (1.2 equiv) in the presence or absence of MeCN (1.2 equiv) in CH₂Cl₂. ^b Isolated yield. ^c Determined by HPLC analysis using a chiral column. ^d The absolute configurations were determined to be *S* by ¹H NMR analysis of corresponding *R*- and *S*-MTPA esters.

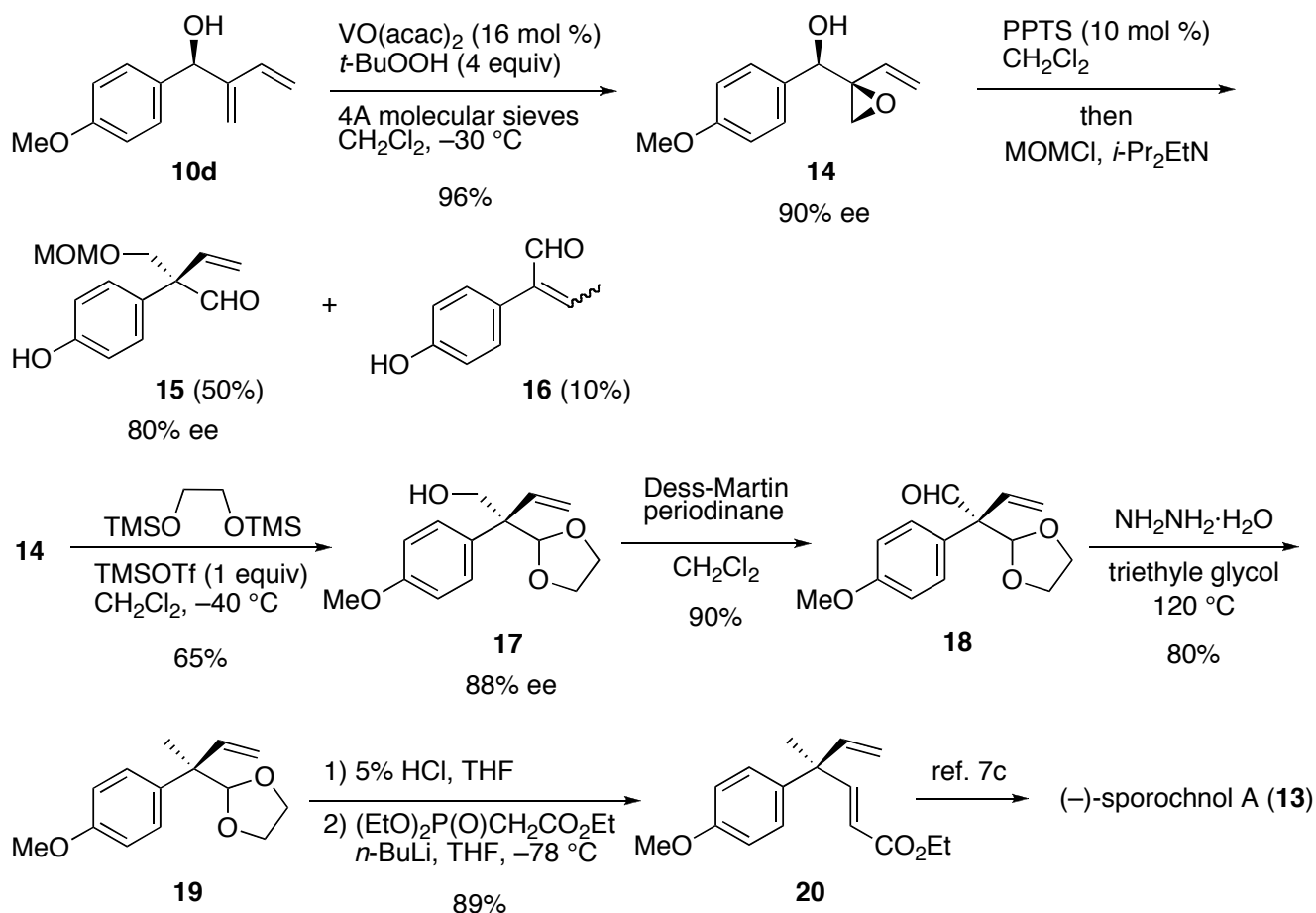
the resulting Ti(IV)-coordinated complex in the reaction media (entry 8). For the reactions of rather sensitive acetals **8b-d** having electron-donating groups, addition of 1.2 equiv of acetonitrile was found to markedly improve the yields of **9**⁹ by attenuating the Lewis acidity of $3\text{TiCl}_4\cdot\text{Ti}(\text{O-}i\text{-Pr})_4$ (entries 4-7). Having established a highly enantioselective route to dienols **10**, we then investigated the synthesis of (–)-sporochinol A (**13**) using **10d**¹⁰ as a chiral building block. It is of importance to provide a promising method for the construction of chiral benzylic quaternary carbon centers, which often occur in biologically intriguing terpenes and alkaloids.¹¹ We envisaged that acid-promoted reaction of epoxy alcohol **11**, available from **10**, would allow us to access compound **12** having a benzylic quaternary carbon center as depicted in Scheme 3. Based on literature precedents,¹² it was anticipated that this rearrangement would take place stereoselectively with inversion of configuration of the quaternary center.



Scheme 3

According to the procedure we established previously,¹³ dienol **10d** was subjected to $\text{VO}(\text{acac})_2$ -catalyzed epoxidation to give epoxide **14** as a single diastereomer in almost quantitative yield. When epoxide **14** (90% ee) was treated with PPTS (0.1 equiv) in CH_2Cl_2 at room temperature followed by methoxymethyl chloride in the presence of Hünig's base in the same flask, the desired product **15** was obtained in 50% yield together with α,β -unsaturated aldehyde **16** (10% yield). However, the enantiomeric purity was eroded to 80% ee from 90% ee (the enantiomeric purity of the starting epoxide **14**), indicating that some racemization took place during the transformation of **14** to **15**. After considerable experimentation, we eventually found conditions where the rearranged product could be obtained without racemization. Thus, upon exposure of **14** to acetalization conditions⁸ using 1,2-di(trimethylsilyloxy)ethane and trimethyl triflate in CH_2Cl_2 at -40°C , acetal **17**¹⁴ of 88% ee was produced in 65% yield. Acetal **17** was then converted to ester **20** via **18** and **19** by a four-step sequence involving Dess-Martin oxidation, Wolff-Kishner reduction, acidic hydrolysis, and Horner-Emmons olefination. The specific rotation, $[\alpha]_{\text{D}}^{18} +17.6$ (*c* 1.00) [lit.^{7c} $[\alpha]_{\text{D}}^{20} +19.6$ (*c* 1.00)], and spectral data of **20** thus obtained was identical with those reported for the precursor of (–)-sporochinol A (**13**) by Fadel and Vandromme^{7c} so that the formal synthesis of **13** was accomplished. At this stage, it was unambiguously proved that the above-mentioned rearrangement of **14** occurred with inversion of configuration of the quaternary center.

In conclusion, the present work provides a highly enantioselective method for the preparation of aryl(1,3-butadien-2-yl)methanols and demonstrates an effective methodology for the construction of a chiral benzylic quaternary carbon center.



Scheme 4

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REFERENCES (AND NOTES)

1. S. Hatakeyama, K. Sugawara, M. Kawamura, and S. Takano, *Tetrahedron Lett.*, 1991, **32**, 4509.
2. For other enantioselective approaches to dienols **5**, see: a) R. Soundararajan, G. Li, and H. C. Brown, *J. Org. Chem.*, 1996, **61**, 100. b) C.-M. Yu, S.-J. Lee, and M. Jeon, *J. Chem. Soc., Perkin Trans. 1*, 1999, 3557. c) J. A. Smulik and S. T. Diver, *Org Lett.*, 2000, **2**, 2271.
3. For a review, see: S. Hatakeyama, *J. Synth. Org. Chem. Jpn.*, 1997, **55**, 793.
4. M. Luo, Y. Iwabuchi, and S. Hatakeyama, *Chem. Commun.*, 1999, 267.
5. M. Luo, Y. Iwabuchi, and S. Hatakeyama, *Synlett*, 1999, 1109.

6. Y.-C. Shen, P. I. Tsai, W. Fenical, and M. E. Hay, *Phytochemistry*, 1993, **32**, 71.
7. For the enantioselective synthesis of sporochinol, see: a) M. Takahashi, Y. Shioura, T. Murakami, and K. Ogasawara, *Tetrahedron: Asymmetry*, 1997, **8**, 1235. b) T. Kamikubo, M. Shimizu, and K. Ogasawara, *Enantiomer*, 1997, **2**, 297. c) A. Fadel and L. Vandromme, *Tetrahedron: Asymmetry*, 1999, **10**, 1153. d) C. A. Luchaco-Cullis, H. Mizutani, K. E. Murphy, and A. H. Hoveyda, *Angew. Chem. Int. Ed.*, 2001, **40**, 1456. e) Y. Kita, A. Furukawa, J. Futamura, K. Ueda, Y. Sawama, H. Hamamoto, and H. Fujioka, *J. Org. Chem.*, 2001, **66**, 8779. f) S. Ohira, A. Kuboki, T. Hasegawa, T. Kikuchi, T. Kutsukake, and M. Nomura, *Tetrahedron Lett.*, 2002, **43**, 4641. g) R. Alibés, F. Busqué, G. G. Bardají, P. de March, M. Figueredo, and J. Font, *Tetrahedron: Asymmetry*, 2006, **17**, 2632.
8. T. Tsunoda, M. Suzuki, and R. Noyori, *Tetrahedron Lett.*, 1980, **21**, 1357.
9. Compound **9d**: $[\alpha]_D^{20}$ -118.8° (*c* 2.68, CHCl_3); FTIR (neat) 3438, 1610, 1510, 1250, 1036 cm^{-1} ; ^1H NMR (300 MHz, CDCl_3) δ 7.29 (d, *J* = 8.4 Hz, 2H), 6.87 (d, *J* = 8.7 Hz, 2H), 6.26 (dd, *J* = 11.1, 17.7 Hz, 1H), 5.39 (brd, *J* = 1.2 Hz, 1H), 5.29 (brs, 1H), 5.23 (dd, *J* = 1.2, 18.0 Hz, 1H), 5.10 (s, 1H), 5.00 (d, *J* = 10.5 Hz, 1H), 4.11-4.01 (m, 1H), 3.87-3.70 (m, 1H), 3.79 (s, 3H), 2.55 (d, *J* = 3.0 Hz, 1H), 1.66-1.51 (m, 2H), 1.24 (d, *J* = 6.3 Hz, 3H), 1.09 (d, *J* = 6.0 Hz, 3H); ^{13}C NMR (75 MHz, CDCl_3) δ 159.3, 146.5, 136.1, 132.2, 128.7, 115.4, 114.9, 113.9, 78.1, 70.2, 64.2, 55.2, 44.5, 23.3, 19.1; HRMS calcd for $\text{C}_{17}\text{H}_{24}\text{O}_3$ (M^+) 276.1725, found 276.1725.
10. Compound **10d**: $[\alpha]_D^{22}$ -85.4° (*c* 0.61, CHCl_3); FTIR (neat) 3417, 1610, 1512, 1252, 1034 cm^{-1} ; ^1H NMR (300 MHz, CDCl_3) δ 7.31 (d, *J* = 8.7 Hz, 2H), 6.88 (d, *J* = 8.7 Hz, 2H), 6.31 (dd, *J* = 11.4, 18.0 Hz, 1H), 5.44 (s, 1H), 5.44 (d, *J* = 3.6 Hz, 1H), 5.33 (s, 1H), 5.17 (d, *J* = 17.6 Hz, 1H), 5.03 (d, *J* = 11.1 Hz, 1H), 3.80 (s, 3H), 1.91 (dd, *J* = 1.7, 3.8 Hz, 1H); ^{13}C NMR (75 MHz, CDCl_3) δ 159.3, 147.7, 136.0, 134.3, 128.3, 115.4, 113.9, 73.5, 55.3; HRMS calcd for $\text{C}_{12}\text{H}_{14}\text{O}_2$ (M^+) 190.0994, found 190.1004.
11. For reviews, see: a) S. F. Martin, *Tetrahedron*, 1980, **36**, 419. b) K. Fuji, *Chem. Rev.*, 1993, **93**, 2037.
12. For reviews, see: a) K. Suzuki, *J. Synth. Org. Chem. Jpn.*, 1988, **46**, 365. b) H. Fujioka, Y. Yoshida, and Y. Kita, *J. Synth. Org. Chem. Jpn.*, 2003, **61**, 133.
13. S. Hatakeyama, K. Sugawara, and S. Takano, *Tetrahedron Lett.*, 1991, **32**, 4513.
14. Compound **17**: $[\alpha]_D^{19}$ -15.8° (*c* 2.10, CHCl_3); FTIR (neat) 3506, 2887, 1601, 1508, 1246, 1028 cm^{-1} ; ^1H NMR (300 MHz, CDCl_3) δ 7.38 (d, *J* = 9.0 Hz, 2H), 6.88 (d, *J* = 9.0 Hz, 2H), 6.05 (dd, *J* = 11.1, 18.0 Hz, 1H), 5.42 (dd, *J* = 1.2, 11.1 Hz, 1H), 5.31 (s, 1H), 5.25 (dd, *J* = 1.1, 17.9 Hz, 1H), 4.07 (ddd, *J* = 6.0, 11.1, 18.3 Hz, 2H), 3.91-1.86 (m, 4H), 3.80 (s, 3H), 2.34 (t, *J* = 6.3 Hz, 1H); ^{13}C NMR (75 MHz, CDCl_3) δ 158.4, 138.4, 131.4, 129.6, 117.7, 113.6, 107.2, 65.5, 65.2, 55.2, 53.1; HRMS calcd for $\text{C}_{14}\text{H}_{18}\text{O}_4$ (M^+) 250.1205, found 250.1200.