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

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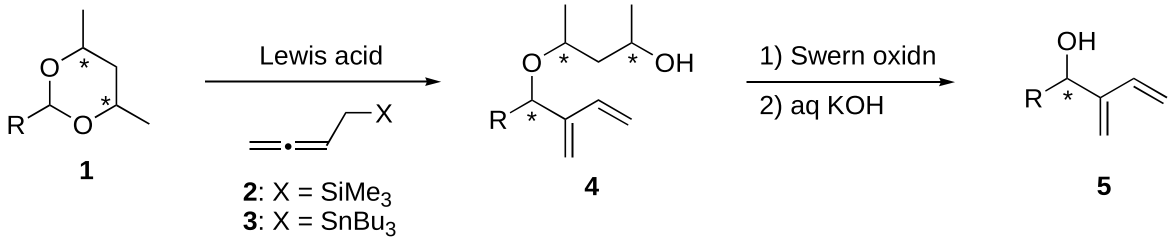
Abstract – Ti(IV)-promoted reaction of the chiral acetals derived from aromatic aldehydes with 1-(tri-*n*-butyl)stannyl-2,3-butadiene followed by removal of the chiral auxiliary gave aryl(1,3-butadien-2-yl)methanols with high enantiomeric purity (>90% ee). The synthetic utility of this method was demonstrated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

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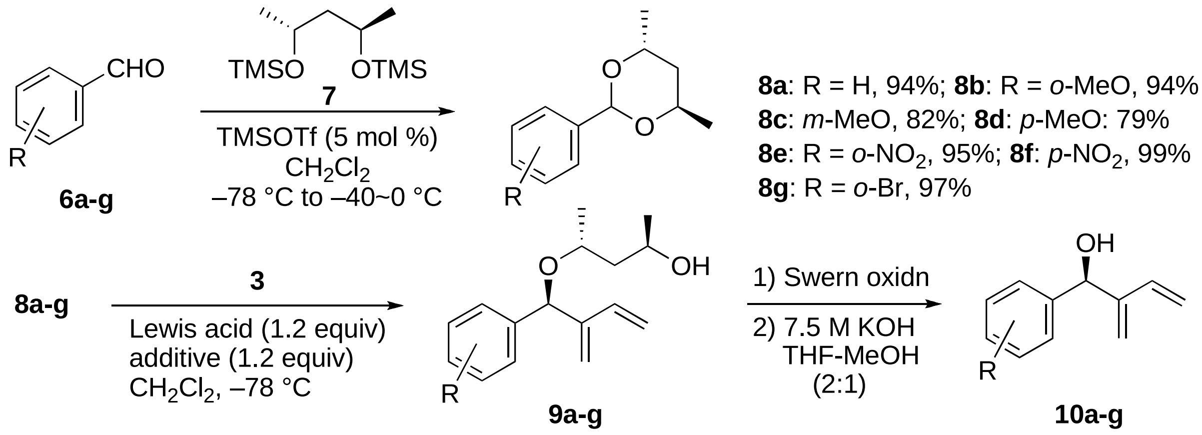
† Dedicated to Professor Emeritus Keiichiro Fukumoto on the occasion of his 75th birthday.

We also demonstrate the utility of this methodology by the formal synthesis of (–)-sporochnol 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 $BF_3{\cdot}Et_2O$ and $3TiCl_4{\cdot}Ti(O\text{-}i\text{-}Pr)_4$ as a promoter according to the procedure[4] 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 ^{1}H NMR analysis of *R*- and *S*-MTPA esters. As can be seen from Table 1, $BF_3{\cdot}Et_2O$ did not promote the dienylation at all in the case of chiral acetals unlike the corresponding dimethyl acetals[4] (entries 1 and 3). On the other hand, $3TiCl_4{\cdot}Ti(O\text{-}i\text{-}Pr)_4$ 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



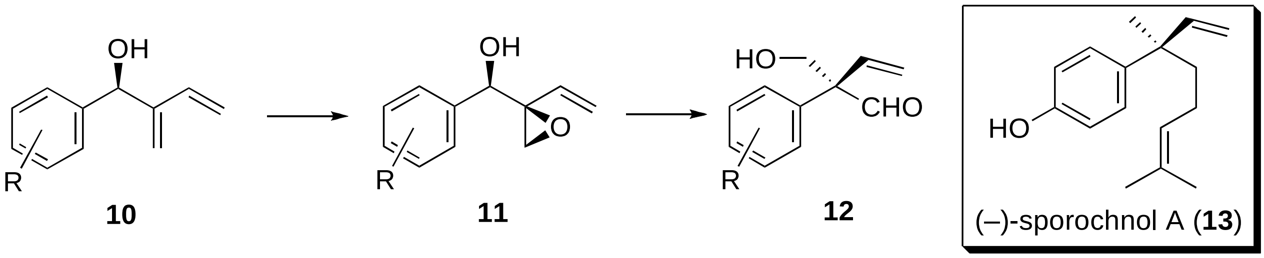
Scheme 2

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**	$BF_3{\cdot}Et_2O$		21	0	—	—
2	**8a**	$3TiCl_4{\cdot}Ti(O\text{-}i\text{-}Pr)_4$		12	70	89	91
3	**8b**	$BF_3{\cdot}Et_2O$		8	0	—	—
4	**8b**	$3TiCl_4{\cdot}Ti(O\text{-}i\text{-}Pr)_4$		5	32	87	78
5	**8b**	$3TiCl_4{\cdot}Ti(O\text{-}i\text{-}Pr)_4$	MeCN	24	76	92	90
6	**8c**	$3TiCl_4{\cdot}Ti(O\text{-}i\text{-}Pr)_4$	MeCN	24	73	90	90
7	**8d**	$3TiCl_4{\cdot}Ti(O\text{-}i\text{-}Pr)_4$	MeCN	24	70	91	90
8	**8e**	$3TiCl_4{\cdot}Ti(O\text{-}i\text{-}Pr)_4$		12	0	—	—
9	**8f**	$3TiCl_4{\cdot}Ti(O\text{-}i\text{-}Pr)_4$		24	82	93	98
10	**8g**	$3TiCl_4{\cdot}Ti(O\text{-}i\text{-}Pr)_4$		24	81	98	91

[a] The 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 CH_2Cl_2. [b] Isolated yield. [c] Determined by HPLC analysis using a chiral column. [d] The absolute configurations were determined to be *S* by ^{1}H NMR analysis of corresponding *R*- and *S*-MTPA esters.

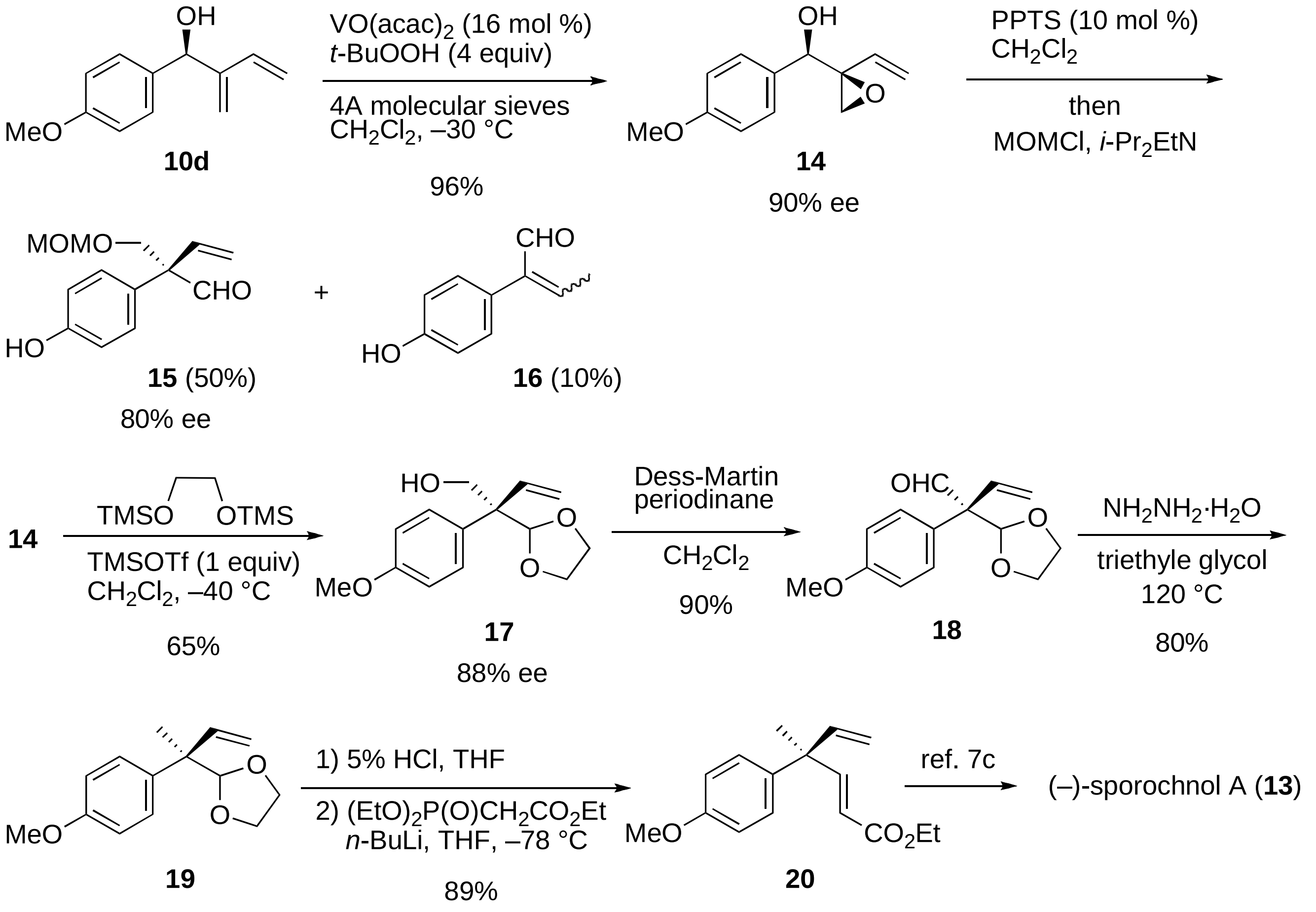
the resulting Ti(IV)-coordinated complex in the reaction media (entry 8). For the reactions of rather sensitive acetals **8b-d** having electron-donating groups, addition of 1.2 equiv of acetonitrile was found to markedly improve the yields of **9**[9] by attenuating the Lewis acidity of $3TiCl_4\cdot Ti(O\text{-}i\text{-}Pr)_4$ (entries 4-7). Having established a highly enantioselective route to dienols **10**, we then investigated the synthesis of (–)-sporochnol 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 $VO(acac)_2$-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 conditions[8] 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, $[\alpha]_D^{18}$ +17.6 (*c* 1.00) [lit.[7c] $[\alpha]_D^{20}$ +19.6 (*c* 1.00)], and spectral data of **20** thus obtained was identical with those reported for the precursor of (–)-sporochnol 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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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 $C_{17}H_{24}O_3$ (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 $C_{12}H_{14}O_2$ (M^+) 190.0994, found 190.1004.

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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 $C_{14}H_{18}O_4$ (M^+) 250.1205, found 250.1200.