Synthetic Methods

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Asymmetric Sequential Allylic Transfer Reaction for the Synthesis of 2-(1-Stannylvinyl)-1,3-diols: Concise Synthesis of (−)-Avenaciolide and (−)-Isoavenaciolide**

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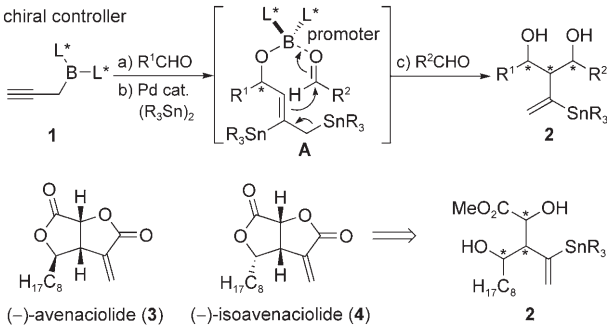
Stereocontrolled consecutive processes can offer advantages over stepwise transformations by increasing chemical efficacy and saving efforts as a result of a simple operation.[1] During the course of our research program aimed at developing new synthetic methods for the stereoselective construction of pyran rings through stepwise allylic transfer reactions,[2] we disclosed our investigations on transition-metal-catalyzed intramolecular allylations mainly between allene and carbonyl functionalities to afford cyclic compounds with high levels of stereoselectivity.[3] With these observations in hand, we became interested in designing a sequential allylic transfer reaction from **1** with two aldehydes to form acyclic 2-(1-stannylvinyl)-1,3-diols **2**, which contain versatile functional groups (Scheme 1).



Scheme 1. General strategy for the synthesis of **2**, and thus natural products **3** and **4**, by a sequential approach. L* = chiral ligand.

It was envisaged that the sequential allylic transfer reaction starting from **1** could be realized by a three-step sequence as shown in Scheme 1. To provide direct access to **2**, we considered the bis(stannyl) compound **A** as a crucial intermediate. The transformation involves propargylboration

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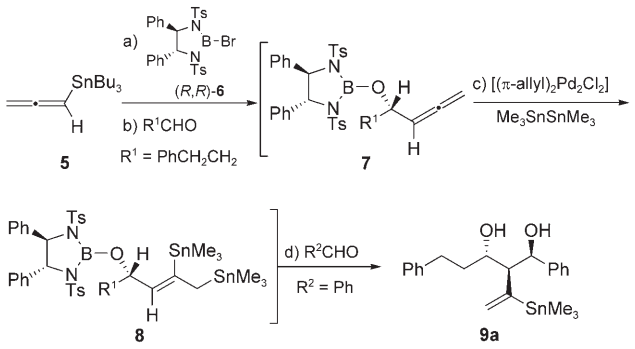
with an aldehyde to yield an allenic species, distannation of the allene moiety using a palladium catalyst to form the allylic tin reagent **A**, and a second allylic transfer reaction with another aldehyde by activation of the existing boronyl group. Thus, the boronyl moiety would play two important roles—as a chiral controller and a Lewis acid promoter—to regulate reactivity and stereoselectivity during the reaction sequence. Herein, we report a one-pot sequential transformation for the stereoselective synthesis of 2-(1-stannylvinyl)-1,3-diols with the generation of three contiguous stereogenic centers, and application of this method to the synthesis of (−)-avenaciolide and (−)-isoavenaciolide in three steps.

We began with **5** and **6** for the first allylic transfer, as developed by Corey et al.,[4] to give easy access to **7** with excellent enantioselectivity (Scheme 2). Initial attempts of a



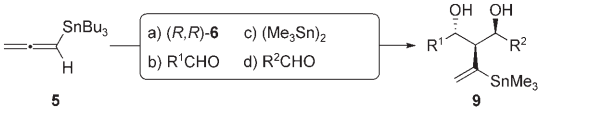
Scheme 2. Preliminary investigations of the asymmetric sequential allylic transfer reaction. Ts = *p*-toluenesulfonyl.

distannation reaction of **7** ($R^1 = PhCH_2CH_2$) with $Bu_3SnSnBu_3$ in the presence of a palladium complex followed by addition to benzaldehyde to give **9a** were unsuccessful under various reaction conditions, presumably owing to a lack of reactivity caused by the steric bulkiness of the tributylstannyl group.[5] We subsequently observed that the use of $Me_3SnSnMe_3$ in the presence of $[(\pi\text{-allyl})_2Pd_2Cl_2]$, which was previously utilized for the cyclization of allene-aldehydes,[3a] could also be employed for this purpose. Upon surveying numerous conditions, the following observations emerged: 1) for the first allylic transfer, the use of 1.3 equivalents of **5** and **6** was optimum to prevent subsequent addition of the same aldehyde; 2) for the distannation reaction, the use of 3 mol% of $[(\pi\text{-allyl})_2Pd_2Cl_2]$ in CH_2Cl_2 at −40 °C for 4 h was most efficient in terms of reaction yields; 3) the formation of **8** was confirmed by NMR spectroscopy after quenching with pH 7 buffer solution; 4) only $Me_3SnSnMe_3$ proved to be effective for the transformation; and 5) the use of CH_2Cl_2 resulted in optimum chemical yields in comparison to other solvents.

Under optimal conditions, the reaction was conducted by dropwise addition of **5** (1.3 equiv) to (*R*,*R*)-**6** (1.3 equiv) at −10 °C in CH_2Cl_2. After 11 h at −10 °C the reaction mixture was cooled to −78 °C, and $PhCH_2CH_2CHO$ (1 equiv) was added during 2 h. To the resulting mixture was then added $Me_3SnSnMe_3$ (1.3 equiv) followed by $[(\pi\text{-allyl})_2Pd_2Cl_2]$ (3 mol%), and the reaction mixture was maintained for 4 h at −40 °C. After cooling to −78 °C, benzaldehyde (1 equiv) was added. Aqueous workup and silica gel chromatography afforded **9a** as a single stereoisomer in 77% isolated yield. Note that although an excess of propargylborane **6** (1.3 equiv) was used, the formation of allenyl carbinol resulting from its reaction with benzaldehyde was not observed. A control experiment clearly revealed that the propargylborane **6** was poisoned during the distannation process presumably by the formation of 2,3-distannylallylborane, which does not react with benzaldehyde at −78 °C.

With the notion that this approach might lead to a general and efficient method, we set out to determine the scope of the reaction (Table 1). Indeed, the method is successful with a

Table 1: Scope of the sequential allylic transfer reaction of **5** and (*R*,*R*)-**6**.[a]

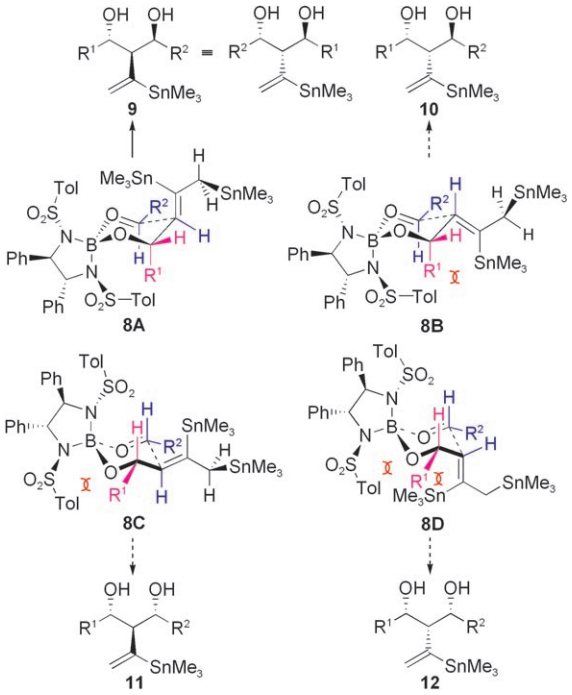


Entry	R^1	R^2	**9**	Yield [%][b]
1	$PhCH_2CH_2$	Ph	**a**	77
2	Ph	$PhCH_2CH_2$	**b**	68
3	$PhCH_2CH_2$	$PhCH_2CH_2$	**c**	78
4	$PhCH_2CH_2$	C_5H_{11}	**d**	81
5	C_5H_{11}	Ph	**e**	73
6	Me_2CHCH_2	C_5H_{11}	**f**	68
7	$PhCH_2CH_2$	Me_2CHCH_2	**g**	71
8	$PhCH_2CH_2$	4-BrPh	**h**	72
9	$PhCH_2CH_2$	$C_3H_7CH{=}CH$	**i**	63
10	Me_2CH	C_5H_{11}	**j**	66
11	$PhCH_2CH_2$	Me_2CH	**k**	74

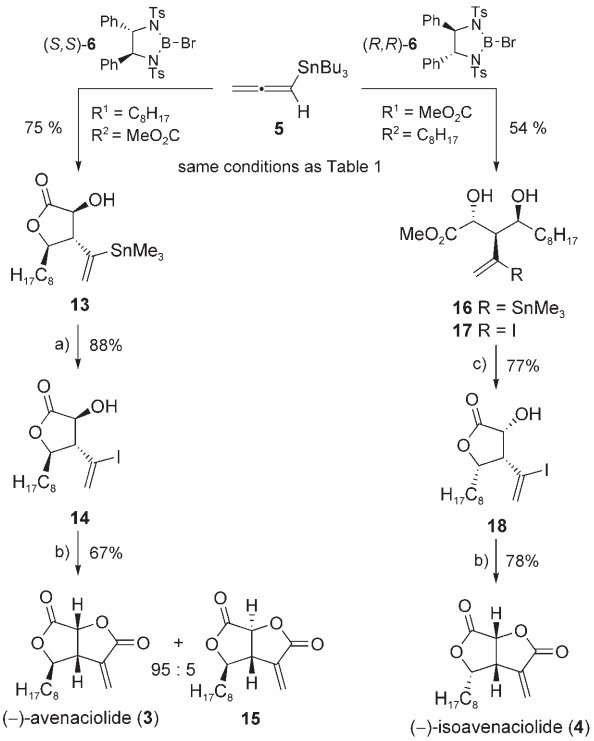
[a] Reactions were run in CH_2Cl_2. Reagents and conditions: a) −10 °C, 11 h; b) −78 °C, 2 h; c) $Me_3SnSnMe_3$ (1.3 equiv), $[(\pi\text{-allyl})_2Pd_2Cl_2]$ (3 mol%), −40 °C, 4 h; d) −78 °C, 4 h. [b] Refers to yield after purification.

variety of aldehydes to yield the 2-(1-stannylvinyl)-1,3-diols **9** in good yields. It is important to note that the reaction produced no, or only detectable amounts (less than 1%), of minor stereoisomers according to analysis by ^1H NMR spectroscopy and HPLC with chiral column (Chiralcel OD-H or OD-RH) in comparison with authentic samples prepared from (*S*,*S*)-**6**.

The stereochemical outcome for the transformations can be explained by the analysis of stereochemical models as depicted in Scheme 3.[6] There are two possibilities governing the stereocontrol of the second allylic transfer reaction. First, the remote stereogenic center attached to R^1 was envisioned to impact stereoselectivity during the allylic transfer through the favored model **8C** for **11**. However, the results obtained (Table 1, entries 1–3) did not support this claim: the stereochemical relationship between **9a** and **9b** turned out to be diastereomeric rather than enantiomeric, and **9c** is an optically active species. Therefore, the preference for the absolute and relative configurations for adducts from (*R*,*R*)-**8** with aldehydes could be explained on the basis of the geometrical preference of the chairlike stereochemical model **8A** (Scheme 3). The stereoselectivity for both the



Scheme 3. Stereochemical routes.



Scheme 4. Synthesis of (−)-avenaciolide (**3**) and (−)-isoavenaciolide (**4**): a) NIS, −78 °C, 2 h, CH_2Cl_2; b) $[Pd(PPh_3)_4]$ (2 mol %), CO (100 atm), K_2CO_3, CH_3CN, 70 °C, 1 h; c) NIS, −78 °C, 1 h, CH_2Cl_2, then CF_3CO_2H (10 mol %), 2 h. NIS = *N*-iodosuccinimide.

first and second allylic transfer reactions must be controlled by the chiral ligand. The exceptional stereoselectivity can also be explained by assuming that a tight coordination of the aldehyde to the boronyl moiety must be required for the formation of the new C–C bond, such that the overlap between the carbonyl group and the double bond leads to optimum stereoelectronic effects and minimum steric repulsions.

In light of the above results for the stereospecific sequential allylic transfer reaction, we next turned our attention to the application of this approach to the synthesis of the natural products (−)-avenaciolide (**3**) and (−)-isoavenaciolide (**4**; Scheme 1), which exhibit antifungal activities.[7] Interestingly, the diastereomer **10** can be obtained simply by changing the addition sequence of the aldehydes as illustrated in Scheme 3. Thus, we envisaged that the enantioselective synthesis of **3** and **4** could be realized by the sequential addition of aldehydes and appropriate selection of the chiral bromoborane **6** to obtain the correct absolute configurations. Even though the C–OH stereogenic center in **13** is not matched with that in **3**, we predicted that it could be epimerized to the desired product owing to the greater thermodynamic stability of a *cis*-fused bicyclic ring relative to the *trans* isomer.

We undertook the synthesis of **3** from the allenylstannane **5** and (*S*,*S*)-**6** as shown in Scheme 4. Lactone **13** was cleanly obtained under standard conditions in 75 % yield through the sequential allylic transfer reaction. Conversion of **13** into **14** was achieved in 88 % yield by using NIS.[8] Surprisingly, our attempts to convert **14** into **3** under a CO atmosphere using palladium catalysis according to standard procedures[9] were not efficient in terms of the desired epimerization from **15** to **3**. For example, treatment of **14** with CO (10 atm) in the presence of $[Pd(PPh_3)_4]$ (2 mol %) and Et_3N in CH_3CN at 50 °C for 5 h afforded **3** and **15** in a ratio of 2:1 (71 %). Longer reaction times resulted in decomposition of the products. Fortunately, we found that modified Stille conditions were effective for our purpose.[10] Thus, treatment of **14** under an atmosphere of CO (100 atm) in the presence of $[Pd(PPh_3)_4]$ (2 mol %) and K_2CO_3 in CH_3CN at 70 °C for 1 h afforded (−)-avenaciolide (**3**, 67 %) along with **15** in a ratio of 95:5 as judged by ^1H NMR spectra of the crude mixture.

We then turned our attention to the synthesis of (−)-isoavenaciolide (**4**). Compound **16** was obtained in moderate (54 %) yield, probably because intramolecular chelation of the boronyl group with the ester in **8** resulted in diminished reactivity with nonanal (12 h at −78 °C; Scheme 4). Treatment of **16** with NIS to obtain the corresponding vinyl iodide **17** afforded a 1:1 mixture of **17** and the lactone **18**. However, after complete consumption of **16** in its reaction with NIS at −78 °C for 1 h, addition of CF_3CO_2H (10 mol %) at −78 °C resulted in the formation of **18** in 77 % yield. A modified Stille reaction of **18** completed the synthesis of **4**.

In summary, we have described a sequential allylic transfer reaction for the synthesis of enantiomerically enriched 2-(1-stannylvinyl)-1,3-diols which provides three contiguous stereogenic centers through a four-component assembly. The approach is efficient and promises to be synthetically useful, as demonstrated here with the concise syntheses of (−)-avenaciolide and (−)-isoavenaciolide.

Experimental Section

General procedure—preparation of **9a** from (*R*,*R*)-**6**: A flame-dried 20-mL Schlenk flask containing (+)-(1*R*,2*R*)-1,2-diphenyl-1,2-bis-*p*-toluenesulfonylamide (0.50 g, 0.96 mmol) was charged with dry CH_2Cl_2 (7 mL), and the resulting mixture was cooled to 0 °C and treated with BBr_3 (1.1 mL of a freshly prepared 1 M solution in CH_2Cl_2, 1.1 mmol). The solution was stirred at 0 °C for 1 h, warmed to 20 °C and maintained at this temperature for 5 h, and then concentrated under vacuum (1 mm Hg). Dryness of the vacuum line was maintained with a drying tube containing anhydrous $CaSO_4$ and two traps (one containing NaOH pellets, and the other a cold trap at −78 °C). Freshly distilled CH_2Cl_2 (5 mL) was added and evaporated under vacuum as above.

Freshly distilled CH_2Cl_2 (4 mL) was again added to the residue, and the homogeneous solution of (*R*,*R*)-**6** was cooled to −10 °C and treated dropwise with 1,2-propadienyl-tributylstannane (**5**, 0.33 g, 1.00 mmol) in CH_2Cl_2 (1 mL). The reaction mixture was maintained at −10 °C overnight (ca. 11 h) and then cooled to −78 °C. A solution of hydrocinnamaldehyde (purified and distilled, 100 mg, 0.74 mmol) in CH_2Cl_2 (1 mL) was added over 10 min to the cooled reaction mixture along the wall of the flask while keeping the temperature below −78 °C. The mixture was then stirred for 2 h, then hexamethyldistannane (0.21 mL, 0.33 g, 1.01 mmol) in CH_2Cl_2 (0.5 mL) was added followed by $[(\pi\text{-allyl})_2Pd_2Cl_2]$ (8.3 mg, 0.022 mmol) in CH_2Cl_2 (0.5 mL). The mixture was then allowed to warm to −40 °C and was stirred for 4 h.

The resulting solution of **8** was cooled to −78 °C, and a solution of benzaldehyde (0.08 mL, 83.6 mg, 0.78 mmol) in CH_2Cl_2 (1 mL) was added dropwise to the flask. The reaction was allowed to proceed for 4 h at −78 °C and then quenched by addition of aqueous buffer solution (pH 7, 10 mL) followed by CH_2Cl_2 (ca. 10 mL) to dissolve the white bis(sulfonamide) precipitate. The aqueous layer was extracted with CH_2Cl_2 (ca. 10 mL × 2), and the combined organic extracts were washed with saturated solutions of $NaHCO_3$ (1 ×) and NaCl (1 ×), dried over anhydrous Na_2SO_4, and filtered. The solvents were evaporated, and the residue was taken up in diethyl ether (ca. 30 mL). The solution was cooled to 0 °C for 20 min to complete the precipitation of (+)-(1*R*,2*R*)-1,2-diphenyl-1,2-bis-*p*-toluenesulfonylamide, which was then removed by filtration through a sintered glass funnel. The filtrate was washed with cold 20% KF solution (1 ×) and saturated aqueous $NaHCO_3$ solution (1 ×). The organic layer was separated, dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure to give the crude product. Final purification was effected by SiO_2 chromatography (4:1 hexanes/EtOAc) to afford pure **9a** as a colorless oil (0.255 g, 0.57 mmol, 77%).

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