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Tetrahedron Letters 49 (2008) 678–681
Tetrahedron Letters

An efficient approach to the stereoselective synthesis of 2,6-disubstituted dihydropyrans via stannyl-Prins cyclization

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Received 28 September 2007; revised 9 November 2007; accepted 21 November 2007

Abstract

A general method has been developed for the stereoselective construction of 2,6-disubstituted dihydropyrans based on the Lewis acid-catalyzed intramolecular reactions of oxocarbenium ions with vinylstannanes. This novel methodology was applied to the enantioselective total synthesis of (−)-centrolobine.

Keywords: Vinylstannanes; Dihydropyrans; Prins cyclization; (−)-Centrolobine

Substituted tetrahydropyrans are common structural motifs of many natural products and biologically active compounds. A number of strategies for their synthesis have been reported.[1] The related 2,6-disubstituted dihydropyran ring system is a particularly attractive target because of its occurrence in natural products and the synthetic usefulness of the olefin function for further functionalization. The latter makes this system a key intermediate in the preparation of many substituted tetrahydropyrans.[2] Some of the most widely used methods for the preparation of dihydropyrans are based on hetero-Diels–Alder cycloadditions,[3] electrophile-initiated alkylation of glycals,[4] olefin metathesis,[5] intramolecular silyl-modified Sakurai reaction,[6] or vinylsilane cyclization of oxocarbenium ions (silyl-Prins cyclizations).[7]

The Prins cyclization is one of the most effective reactions for the synthesis of oxacyclic rings.[8] Most Prins cyclizations involve coupling of homoallylic alcohols with simple aldehydes under acid catalysis. Considerable effort has been directed towards improving the efficiency of the Prins cyclization, mainly by increasing the nucleophilicity of the alkene reagent. If the alkene moiety in the homoallylic alcohol bears a silyl substituent, the reaction can be terminated following cyclization by elimination of the silyl group, leading to the unsaturated product.[9]

Herein, we report that (*Z*)-vinylstannanes of type **1** participate in highly diastereoselective Prins cyclizations with oxocarbenium ions *en route* to 2,6-disubstituted dihydropyrans **2**. Moreover, we also demonstrate, in the context of a total synthesis of (−)-centrolobine (**3**) (Scheme 1), that the necessary Prins cyclization substrates can be quickly assembled from readily available optically pure epoxides.[10]

The preparation of vinylstannanes of type **1** required for the Prins cyclization was easily accomplished by the regio- and stereoselective hydrostannylation of terminal alkynes **4** bearing a hydroxyl group at the homopropargylic position (Scheme 2).[11]

The vinylstannanes **1** thus prepared were reacted with various aldehydes in the presence of TMSOTf[12] at −78 °C in Et_2O to afford the corresponding 2,6-disubstituted dihydropyrans **2** (Table 1).[13]

The Lewis acid used above (TMSOTf) has previously been shown to be effective at catalyzing Prins cyclizations.[14] In most cases, as shown in Table 1, good chemical yields and appreciable cis selectivities, verified by the qualitative NOE enhancements, were obtained. The stereochemical

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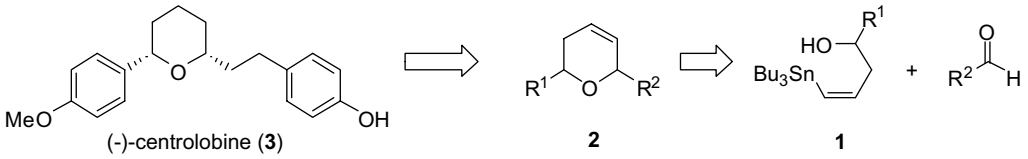
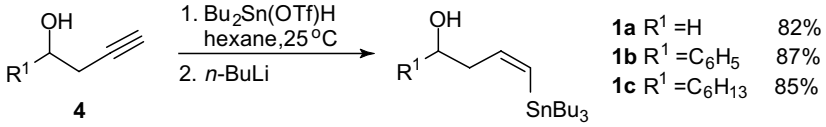
doi:10.1016/j.tetlet.2007.11.128

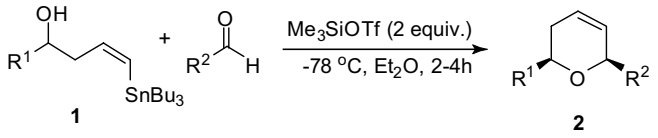


Scheme 1.



Scheme 2.

Table 1
Synthesis of 2,6-disubstituted dihydropyrans



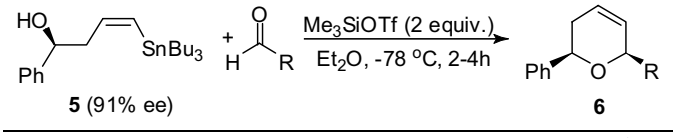
Entry	R^1	R^2	Yield of **2**[a] (%)	cis/trans[b]
1	H	C_6H_5	92	—
2	H	$C_6H_5(CH_2)_2$	86	—
3	C_6H_5	C_6H_5	94	Cis only
4	C_6H_5	*p*-BrC_6H_4	80	Cis only
5	C_6H_5	*p*-$TsOC_6H_4$	93	Cis only
6	C_6H_5	*p*-$MeOC_6H_4$	80	3.5:1
7	C_6H_5	$C_6H_5(CH_2)_2$	76	Cis only
8	C_6H_5	*c*-C_6H_{11}	72	Cis only
9	C_6H_5	C_6H_{13}	87	Cis only
10	C_6H_{13}	C_6H_5	91	Cis only
11	C_6H_{13}	*p*-BrC_6H_4	86	Cis only
12	C_6H_{13}	*p*-$MeOC_6H_4$	78	2:1
13	C_6H_{13}	*p*-$TsOC_6H_4$	87	Cis only
14	C_6H_{13}	$C_6H_5(CH_2)_2$	83	Cis only
15	C_6H_{13}	*c*-C_6H_{11}	69	Cis only

[a] All yields are based on isolated product after purification by column chromatography.
[b] The ratio of products was determined by ^{1}H NMR (500 MHz).

outcome of this reaction is in accord with previous observations and with the expectation that cyclization should occur via a chair-like transition state with R^1 and R^2 disposed equatorially and with initial formation of an (*E*)-oxocarbenium ion.[7,13] It should be noted that the electron density in the aromatic ring of the aryl-substituted oxocarbenium ions appears to have a significant influence on the diastereomeric ratio (see entries 6 and 12). Such a result could be ascribed to the*E*/*Z* isomerization of the respective oxocarbenium ions.[7c,15]

In the case of the series of cyclization experiments presented in Table 1 we used racemic starting materials. The use of optically pure starting material **5** produced optically

Table 2
Prins cyclization of **5** with various aldehydes



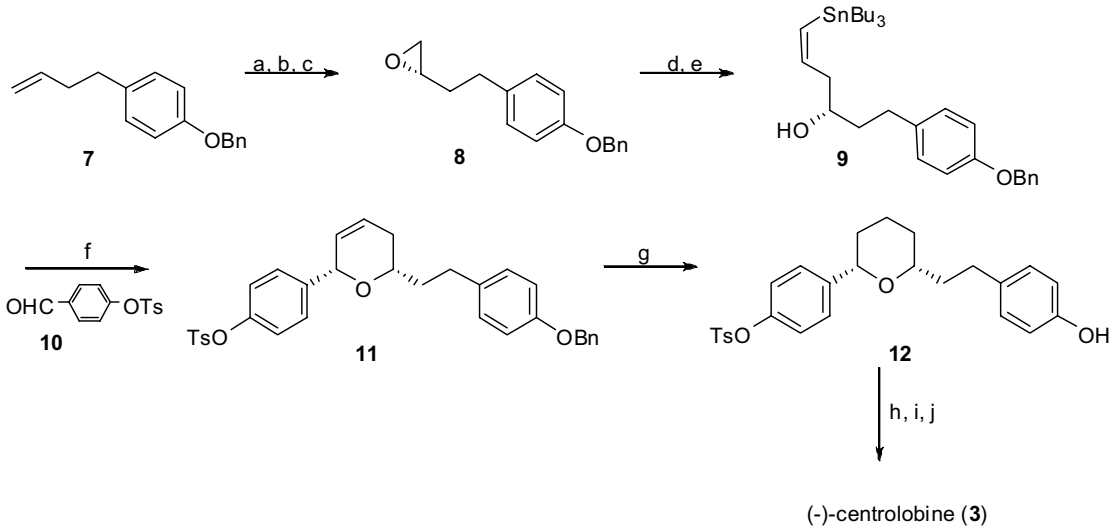
Entry	R	Yield of **6**[a] (%)	ee[b] (%)
1	C_6H_5	95	91
2	*p*-BrC_6H_4	88	91
3	*p*-$TsOC_6H_4$	95	91
4	$C_6H_5(CH_2)_2$	80	87

[a] All yields are based on isolated product after purification by column chromatography.
[b] Determined by HPLC analysis employing Daicel chiral columns.

pure 2,6-disubstituted dihydropyrans **6** without racemization (Table 2).

Finally, we applied our methodology to the total synthesis of the natural product (−)-centrolobine (**1**), an antibiotic isolated from the heartwood of *Centrolobium robustum*.[16] The total synthesis of this natural product has been reported previously by several research groups.[17] The synthetic strategy employed by us is outlined in Scheme 3.

The starting enantiomerically enriched epoxide **8** was prepared from the corresponding olefin **7** via Sharpless asymmetric dihydroxylation[18] followed by tosylation of the primary hydroxyl group and NaOH treatment. The optical purity of **8** was found to be 90% ee by chiral HPLC and the absolute configuration of the intermediate chiral diol was established by CD-spectroscopy.[19] The ring opening of epoxide **8** with lithium acetylide–ethylenediamine complex in DMSO and subsequent hydrostannylation[11] afforded alcohol **9** in a good yield (60% over two steps). The Prins cyclization of **9** with 4-tosyloxybenzaldehyde (**10**) in the presence of TMSOTf yielded dihydropyran **11** in 87% yield. The structure and stereochemistry of the cyclized product **11** were confirmed unambiguously by



Scheme 3. Reagents and conditions: (a) AD-mix-α, *t*-BuOH–H_2O, 0 °C, 80%, 90% ee; (b) TsCl, pyridine, 0 °C, 88%; (c) NaOH, Et_2O–H_2O, 93%; (d) lithium acetylide–EDA, DMSO, 0 °C, 83%, 87% ee; (e) $Bu_2Sn(OTf)H$ then *n*-BuLi, 72%; (f) **10**, TMSOTf (2.0 equiv), Et_2O, −78 °C, 87%; (g) Pd/C, H_2, EtOAc, 78%; (h) TBSCl, imidazole, 95%; (i) Mg (10 equiv), MeOH, 25 °C, 50%; (j) NaH, MeI, THF then Bu_4NF, THF, 0 °C, 73% (over two steps).

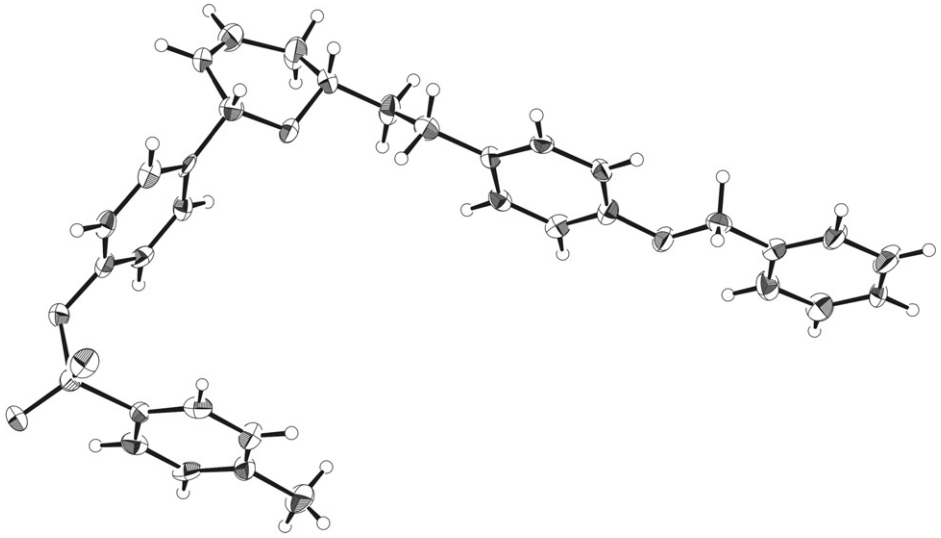


Fig. 1. The X-ray structure of **11**.

single-crystal X-ray analysis (Fig. 1).[20] Catalytic hydrogenation removed the olefin double bond and cleaved the benzyl ether leading to the tetrahydropyran **12** in 78% yield. Subsequent protection of the phenol group as the TBS ether followed by detosylation,[21] methylation and deprotection of the silyl ether afforded (−)-centrolobine in a 15% overall yield. The physical and spectroscopic data obtained for compound **3** were in full agreement with the literature.[15,22]

In conclusion, we have developed a simple approach to functionalized 2,6-dihydropyrans and demonstrated the utility of this methodology by the enantioselective synthesis of (−)-centrolobine. The utilization of this strategy in synthesis of the other natural tetrahydropyrans is underway and will be reported in due course.

Acknowledgement

The authors would like to express our sincere gratitude to Dr. I. Justyniak (Institute of Physical Chemistry PAS) for X-ray crystallographic analysis.

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12. The other Lewis acids generally did not exhibit reactivity compared to that of TMSOTf, furnishing the same product, but in appreciably lower yields.
13. Typical experimental procedure for the trimethylsilyl trifluoromethanesulfonate mediated reaction: To a solution of vinylstannane (0.1 mmol) and aldehyde (0.15 mmol) in Et_2O (5 mL) at −78 °C, under argon, TMSOTf (0.2 mmol) was added dropwise. The reaction was stirred at −78 °C for 2–4 h. After completion of the reaction (TLC), the solution was allowed to warm to 0 °C, then poured into a saturated aqueous solution of $NaHCO_3$ (10 mL) and extracted with Et_2O (2 × 10 mL). The combined organic layers were dried over $MgSO_4$ and the solvent was removed under reduced pressure to give the crude product, which was purified by flash column chromatography (typically hexane/Et_2O 98:2).
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20. Crystallographic data for structure **11** in this Letter have been deposited with the Cambridge Crystallographic Data Centre as Supplementary Publication Number CCDC 662516. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK [fax: +44 1223 336033 or e-mail: deposit@ccdc.com.ac.uk].
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22. Compound **3**: solid, mp 86–87 °C; $[\alpha]_D$ −90.3 (*c* 0.9, $CHCl_3$); lit.[16a]; mp 84–86 °C; $[\alpha]_D$ −93.1 (*c* 0.19, $CHCl_3$); IR (neat) cm^{-1} 3391, 3012, 2935, 1614, 1515, 1445, 1367, 1247, 1176, 887 cm^{-1}; ^1H NMR (500 MHz, acetone-d_6) δ (ppm): 8.07 (s, 1H), 7.32–7.29 (m, 2H), 7.04–6.99 (m, 2H), 6.90–6.86 (m, 2H), 6.74–6.71 (m, 2H), 4.30 (dd, $J = 11.3$, 2.2 Hz, 1H), 3.78 (s, 3H), 3.44 (m, 1H), 2.72–2.57 (m, 2H), 1.94–1.60 (m, 6H), 1.43 (m, 1H), 1.29 (m, 1H); ^{13}C NMR (125 MHz, acetone-d_6) δ (ppm): 159.8, 156.1, 137.1, 133.9, 130.1, 127.7, 115.8, 114.2, 79.9, 77.7, 55.4, 39.5, 34.7, 32.5, 32.1, 31.4; HRMS (ESI) *m*/*z*: $(M+Na)^+$ calcd for $C_{20}H_{24}O_3Na$, 335.1618; found, 335.1603.