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Use of furans in synthesis of bioactive compounds*

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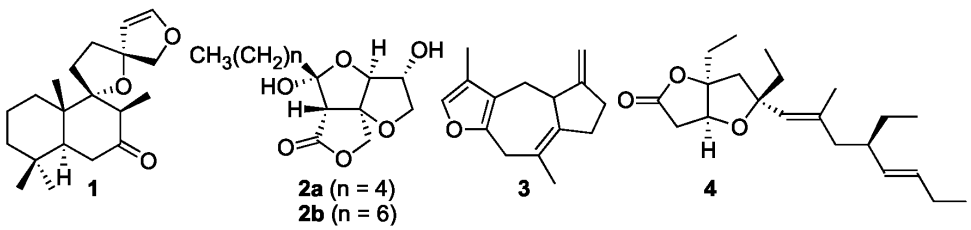
Abstract: Synthetic approaches to the total synthesis of plakortone B, as well as diastereoselective nucleophilic additions to furyl aldehyde and furyl sulfonylimine employing chiral 3-boronates as auxiliary are presented.

Furan is produced by gas-phase decarbonylation of furfural, which, in turn, is prepared in industrial quantities through acid treatment of vegetable residues from the manufacture of porridge oats and cornflakes [1]. In addition, acid-induced elimination of three moles of water from D-fructose also generated hydroxymethylfurfural, which, as one of the few "petrochemicals" readily available from renewable resources, is an extremely versatile six-carbon building block of many useful organic molecules [2]. Our own research programs in the quest of natural and non-natural molecules lately have centered around the use of furan or substituted furans as precursor [3]. In this connection, we have recently completed the total synthesis of several naturally occurring compounds such as prehispanolone **(1)** [4], syringolides 1 (**2a**) and 2 (**2b**) [5], and echinofuran (**3**) [6].



In this article, we wish to discuss our synthetic approaches to the total synthesis of plakortone B (**4**) [7], which was isolated and identified via a bioassay-guided fractionation of the ethyl acetate extract of Jamaican marine sponge *Plakortis halichondrioides* [8]. It was reported that **4** belongs to a novel class of activators of cardiac sarcoplasmic reticulum —Ca^{2+}-pumping ATP synthase at μM concentration [8]. Our synthetic attempts commenced from 3-bromofuran (**5**) [9] and the chiral aldehyde (**6**) [10] as precursors. The synthetic steps are shown in the following scheme. It is noteworthy that **6** is available readily from D-mannitol which is widespread in plants and plant exudates. It can also be obtained from seedweeds and manna (dried exudation of *Fraxinus ornus* L. that contains 40–60 % of mannitol). Electrolytic reduction of glucose also led to the formation of mannitol.

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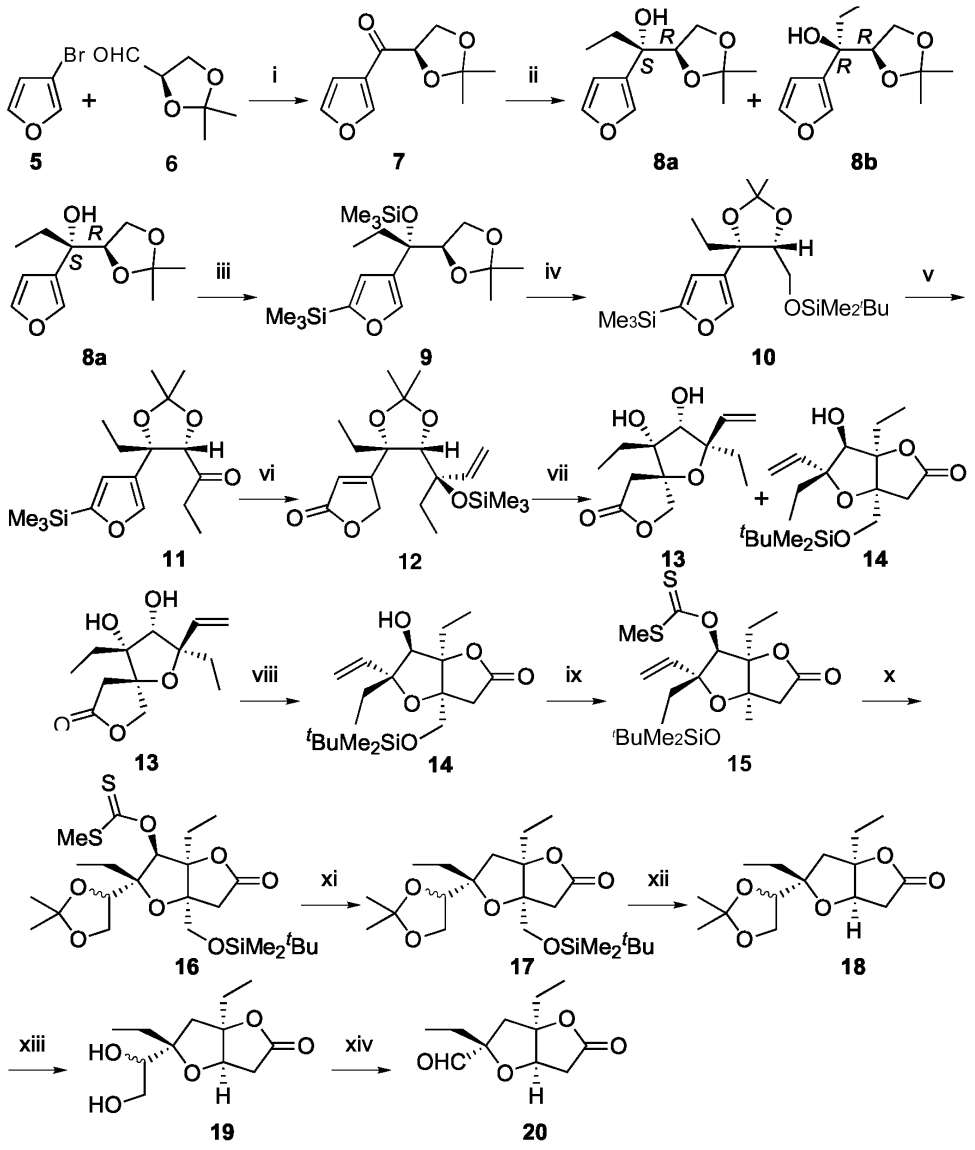
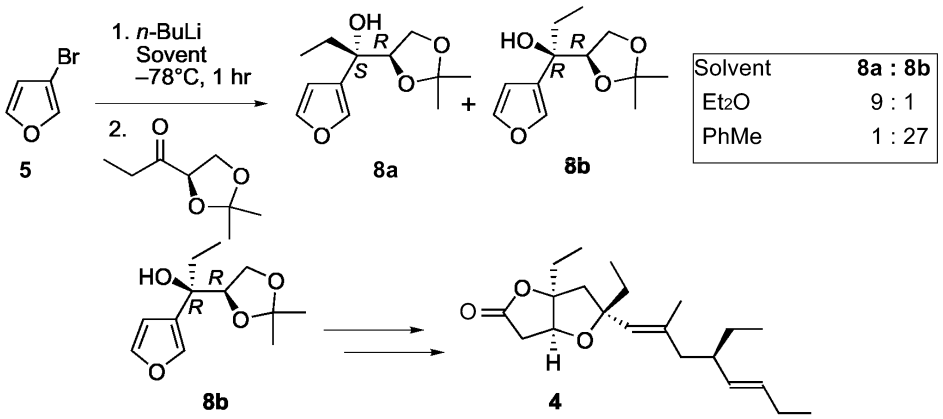


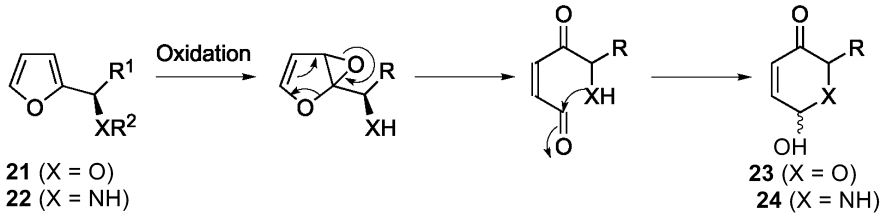
Reagents and conditions: (i) (a) *n*-BuLi, THF, –78 °C, 1 h, then **6,** 68 %, (b) PDC, 4 Å MS, CH_2Cl_2, 24 h, 90 %; (ii) EtMgBr, Et_2O, 0 °C, 78 % **8a:8b** = 15:1; (iii) (a) Me_3SiCl, imidazole, DMAP, DMF, 15 min. 88 %, (b) *n*-BuLi (2.2 equiv), THF, –78 °C, 30 min, then Me_3SiCl (1 equiv), –78 °C, 30 min, 79 %; (iv) (a) 80 % HOAc, 24 h, 99 %, (b) *t*-$BuMe_2SiCl$, imidazole, DMAP, THF, 0 °C, 2 h, (c) $Me_2C(OMe)_2$, *p*-TsOH, THF, reflux, 24 h, 85 %; (v) (a) 0.1 M *n*-Bu_4NF, THF, 0 °C, 30 min, 90 %, (b) PDC, 4 Å MS, CH_2Cl_2, 24 h, (c) EtMgBr, THF, 0 °C, 10 min, (d) PDC, 4 Å MS, CH_2Cl_2, 24 h, 72 %; (vi) (a) CH_2=CHLi, C_6H_{14}, –90 °C A –50 °C, 72 %, (b) Me_3SiCl, imidazole, DMAP, 24 h, (c) 40 % $MeCO_3H$, NaOAc, CH_2Cl_2, 0 °C A r.t., 48 h, 55 %; (vii) (a) 80 % HOAc, 24 h, 99 %, (b) Et_3N, PhMe, reflux, 24 h, (c) 2N HCl, MeOH, 48 h, (d) *t*-$BuMe_2SiCl$, imidazole, DMAP, DMF, 24 h, **13** (50 %), **14** (20 %); (viii) (a) DBU, PhMe, reflux, 3 days, (b) 2N HCl, MeOH, 48 h, (c) *t*-$BuMe_2SiCl$, imidazole, DMAP, DMF, 24 h, 80 %; (ix) (a) NaH, THF, 0 °C, 10 min, (b) CS_2, THF, 0 °C, 10 min, (c) MeI, THF, 0 °C, 30 min, 95 %; (x) (a) OsO_4 (0.1 equiv), NMO, Me_2CO, H_2O, 3 days, (b) $Me_2C(OMe)_2$, *p*-TsOH, THF, 8 h, 90 %; (xi) *n*-Bu_3SnH, AIBN, C_6H_6, reflux, 8 h, 98 %; (xii) (a) *n*-Bu_4NF, THF, 30 min, 98 %, (b) Dess–Martin periodinane, CH_2Cl_2, 24 h, 85 %, (c) $Rh(PPh_3)_3Cl$, *p*-xylene, reflux, 48 h, 80 %; (xiii) 80 % HOAc, 24 h, 99 %; (xiv) $NaIO_4$, CH_2Cl_2, H_2O, 30 min, 95 %.

As shown below [7b], ketone **7** was prepared from **5** and **6** through a bromo-lithium exchange protocol. Nucleophilic addition of ethylmagnesium bromide led to a mixture of **8a** and **8b** in the ratio of 15:1, presumably through a chelation model [7a]. Owing to the unknown absolute configuration of **4**, we arbitrarily chose the major product **8a** as our starting material. Protection of the hydroxy group of **8a**, and a regioselective silylation route furnished **9**, which was allowed to undergo a series of deprotection and protection steps to provide **10**. Again, deprotection, nucleophilic addition of EtMgBr, and subsequent oxidation gave ketone **11**. A non-chelation control addition of vinyllithium and oxidation of the 2-silylated furan eventually led to the formation of butenolide **12.** A conjugate addition promoted by triethylamine followed by intramolecular transesterification and protection of the primary hydroxy group nonetheless provided **14** in a meager yield, together with **13**, which was unable to undergo transesterification due to the *anti*-disposition of the lactone and the hydroxy group. It is noteworthy that the protection step was essential because only in this way, the chromatographic separation of **13** and **14** was convenient due to their polarity difference. DBU was found to promote the ring-opening and ring-closure of **13**, and as a result, 80 % of **14** was obtained after similar work-up procedures. With **14** in hand, the next step was to remove the hydroxy group, which had been in our program rather important for the assignment of absolute configuration to **14** owing to its known *R*-configuration as originated from mannitol. However, it was found that after the formation of **15** from **14**, the double bond of **15** must be protected before the execution of the radical reaction. Thus, oxidation and acetonide formation was followed by a radical-induced reaction to remove the oxygenated functionality, giving **17**. Finally, removal of the acetonide and oxidative cleavage of the resulting diol afforded the aldehyde product **20.** At this stage, the absolute stereochemistry of plakortone D was identified through its total synthesis by Kitching [11], and, unfortunately, **20** was found to be enantiomeric to the natural series. In light of this, we turned our attention to the synthesis of natural **4** by starting from **8b**.

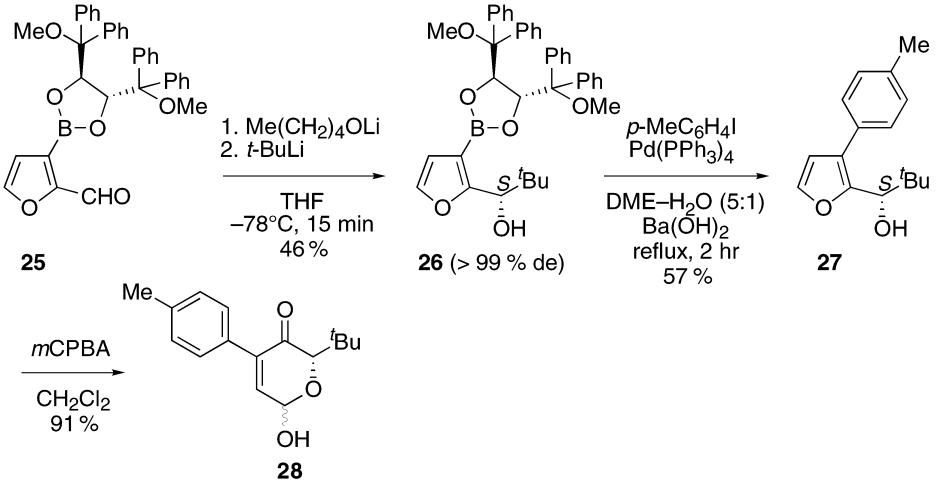
It was desired to look for a new procedure so that **8b** could be realized as the major product. Fortunately, it was uncovered that **8a** was obtained as the major product through the reaction in diethyl ether between 3-lithiofuran and the ethyl ketone as depicted in the scheme below, presumably due to an intermediate with efficient chelation [7a]. While in toluene, a non-chelation model was preferred so that our desired **8b** was generated [7a]. We are now attempting to synthesize from **8b** the enantiomer of **20** as the key precursor in the quest of **4.**



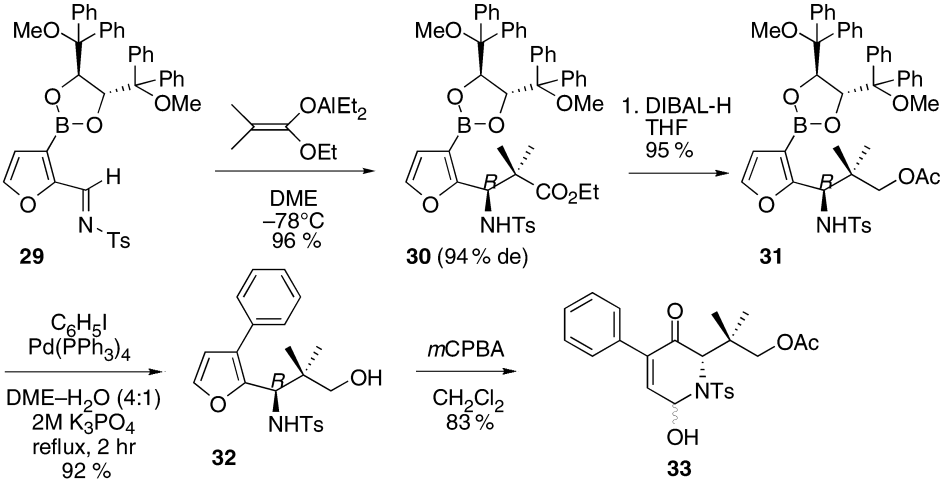
Oxidative rearrangements of furylmethanols **21** and furylmethylamines **22** are effective procedures from which 6-hydroxy-2*H*-pyran-3(6*H*)-ones **23** and 6-hydroxy-1,6-dihydro-2*H*-pyridin-3-ones **24** are obtained, respectively [12].



In the following scheme [13], we made use of the chiral boronate [14] substituted at C-3 of the furfural **25** to direct the nucleophilic addition of *t*-BuLi. The resulting diastereomeric mixture was easily and efficiently separated by silica gel column chromatography to lead to the diastereomerically pure furylmethanol **26**, which was then allowed to undergo a Suzuki cross-coupling to form **27**. Subsequently, an oxidative rearrangement converted **27** to the optically pure hydroxypyranone **28**. The additive lithium pentoxide was believed to add initially to boron atom, thereby leading to the *S*-enantioselection [13]. In this program, the chiral boronate functioned first as a chiral director, and finally as an organoboron substrate for the Suzuki reaction.



The following scheme demonstrated our recent result on the diastereoselective addition reactions of furyl sulfonylimine using again chiral boronates as auxiliary [15].



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