ORGANIC LETTERS

2006
Vol. 8, No. 15
3343−3345

Regioselective Pd-Catalyzed Synthesis and Application of 3-Methyl-5-bromo-2-pyrone toward Keto-phomactin A

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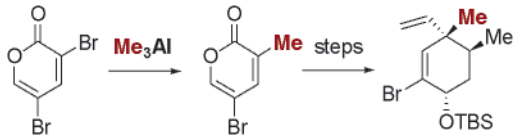
Received May 19, 2006

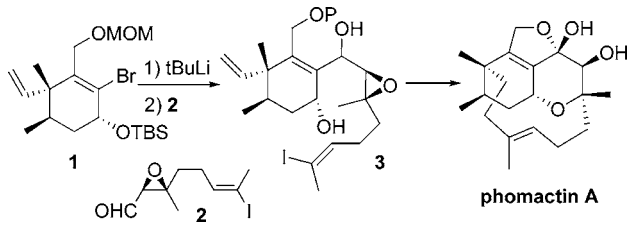
ABSTRACT



An efficient one-step synthetic protocol for 3-methyl-5-bromo-2-pyrone was developed using the C3-selective Pd-catalyzed coupling reaction of 3,5-dibromo-2-pyrone with Me_3Al–dimethylaminoethanol complex. A subsequent seven-step reaction sequence provided a cyclohexenyl bromide, which served as the key intermediate for the synthesis of the keto analogue of phomactin A, in 31% overall yield.

Phomactin A, isolated from *Phoma* sp. in the early 1990s[1] features a tricyclic furanochroman skeleton integrated into a 12-membered macrocycle. In addition to its unique structural profile, it has a wide spectrum of intriguing physiological functions including PAF (platelet activating factor) antagonistic activity that have triggered intensive synthetic studies on this compound over recent years.[2] Owing to its structural complexity, its total synthesis was achieved only recently in racemic form by Pattenden et al.[2a,c] and later in asymmetric form by Halcomb et al.[2b] In Halcomb's synthesis, the lithiated cyclohexene core **1** was added to aldehyde **2** to construct **3**. Subsequent synthetic operations, including an intramolecular B-alkyl Suzuki coupling reaction,[3] completed the first asymmetric total synthesis of (+)-phomactin A (Scheme 1).[2b]

Scheme 1



Studies seeking further insight into the biological functions are hampered by the lengthy synthetic route to phomactin A and its analogues. The synthesis of the cyclohexene core **1** required 18 steps from (+)-pulegone and proceeded in 4.8% overall yield. As a result, we became interested in synthesizing the keto form of phomactin A, devoid of the cyclic ketal unit, because it could be a versatile synthetic platform for facile derivatization into the related analogues, in addition to having its own potential activities. Moreover, the requisite cyclohexenyl bromide **4** could readily be prepared from the Diels−Alder cycloaddition of 3-methyl-

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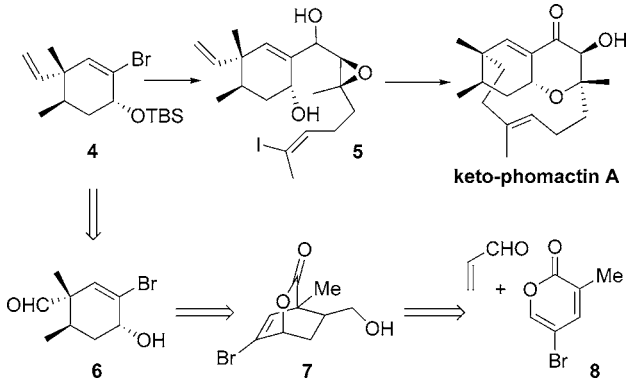
10.1021/ol061231z CCC: $33.50
Published on Web 06/30/2006

5-bromo-2-pyrone with acrolein, providing all the necessary functionality with appropriate relative stereochemistry (Scheme 2). Incorporation of **4** into the Halcomb's elegant synthetic

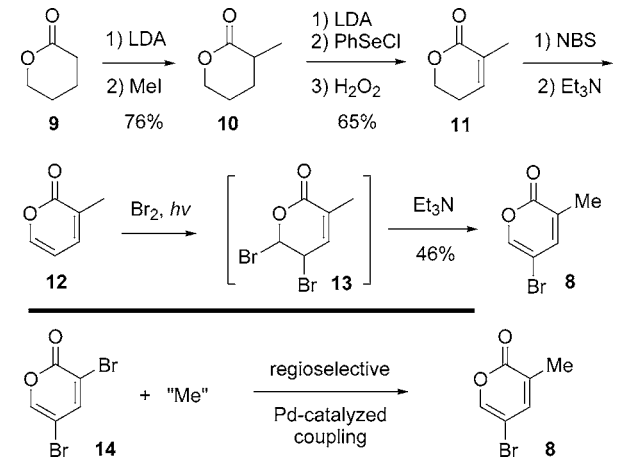
Scheme 2



sequence would furnish keto-phomactin A.

The preparation of 3-methyl-5-bromo-2-pyrone **8** was reported by Meinwald and co-workers, starting from *δ*-valerolactone **9** in 5 steps with an overall yield of 12% (Scheme

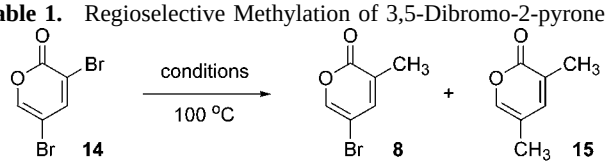
Scheme 3



3).[4] It was subsequently used for the synthesis of supellapyrone, a sex pheromone of the brownbanded cockroach, as well as its related stereoisomers, via coupling reactions with alkylzinc reagents.[4] We envisaged preparing 3-methyl-5-bromo-2-pyrone **8** readily in one step from 3,5-dibromo-2-pyrone **14**[5] via a Pd-catalyzed C3-selective methylation reaction. Presented herein are efficient syntheses of 3-methyl-5-bromo-2-pyrone **8** and the cyclohexene intermediate **4**.

We first explored the coupling reaction with tetramethyltin under the conditions previously shown to be C3-selective.[6] The reaction provided the desired coupling product **8**, but in 31% yield (entry 1). The coupling reaction with 1.1 equiv of trimethyl boroxine (TMB) afforded disubstituted 3,5-dimethyl-2-pyrone **15**, as the sole product, in 36% yield, indicating participation of more than one Me group of TMB in the reaction. Use of 0.4 equiv of TMB provided no significant improvement (entry 4). The coupling with methyl boronic acid under the usual Suzuki conditions was not satisfactory (entry 5). Neither Kumada[7] nor Negishi[8] coupling reactions proved effective (entries 6 and 7). We observed substantial decomposition of the starting 2-pyrone in both cases. Much better results were obtained when Me_3Al (2 M solution in toluene) was employed as a coupling partner. The stoichiometric use of Me_3Al produced the disubstituted product **15** in 85% yield (entry 10). Contrary to entry 4, we obtained 3-methyl-2-bromo-2-pyrone **8** in 72% yield when 0.4 equiv of Me_3Al was used (entry 11). The consistent take-up of the right amount of Me_3Al proved rather cumbersome because of the reactive nature of Me_3Al. The prior complexation of Me_3Al with dimethylaminoethanol made its handling much easier, providing **8** in a reproducible yield of 85% (entry 12).[9] The transformation of **8** into the

Table 1. Regioselective Methylation of 3,5-Dibromo-2-pyrone



entry	conditions	**8**:**15**[a] (yield[b])
1	Me_4Sn (1.2 eq), $PdCl_2[P\text{-}(o\text{-}tolyl)_3]_2$, tol, 48 h	100:0 (31%)
2	Me_2SnCl_2 (1.2 eq), $Pd(PPh_3)_4$, tol, 24 h	100:0 (32%)
3	TMB[c] (1.2 eq), $Pd(PPh_3)_4$, tol, 48 h	0:100 (36%)
4	TMB (0.4 eq), $PdCl_2[P\text{-}(o\text{-}tolyl)_3]_2$, dioxane, 48 h	33:67 (22%)
5	$MeB(OH)_2$ (1.2 eq), $PdCl_2(PPh_3)_2$, tol, 48 h	65:35(30%)
6	MeMgBr (1.2 eq), $PdCl_2(PPh_3)_2$, tol, 24 h, rt	N/A (trace)
7	MeZnCl (1.2 eql, $Pd(PPh_3)_4$, THF, rt, 12 h	N/A (trace)
8	Me_2Zn (1.2 eq), $PdCl_2(PPh_3)_2$, dioxane, 1 h	86:14 (35%)
9	Me_2Zn (0.7 eq), $PdCl_2(PPh_3)_2$, tol, 1 h	100:0 (37%)
10	Me_3Al (1.2 eq), $PdCl_2(PPh_3)_2$, tol, 1.5 h	0:100 (85%)
11	Me_3Al (0.4 eq), $PdCl_2(PPh_3)_2$, tol, 1.5 h	100:0 (72%)
12	0.4 eq. Me_3Al[d], $PdCl_2(PPh_3)_2$, tol, 1.5 h	100:0 (85%)

[a] Ratio of crude products by ^1H NMR. [b] Combined yield. [c] Trimethyl boroxine. [d] Dimethylaminoethanol complex was used.

cyclohexene intermediate **4** (Scheme 4) began with the Diels−Alder cycloaddition with acrolein, which produced

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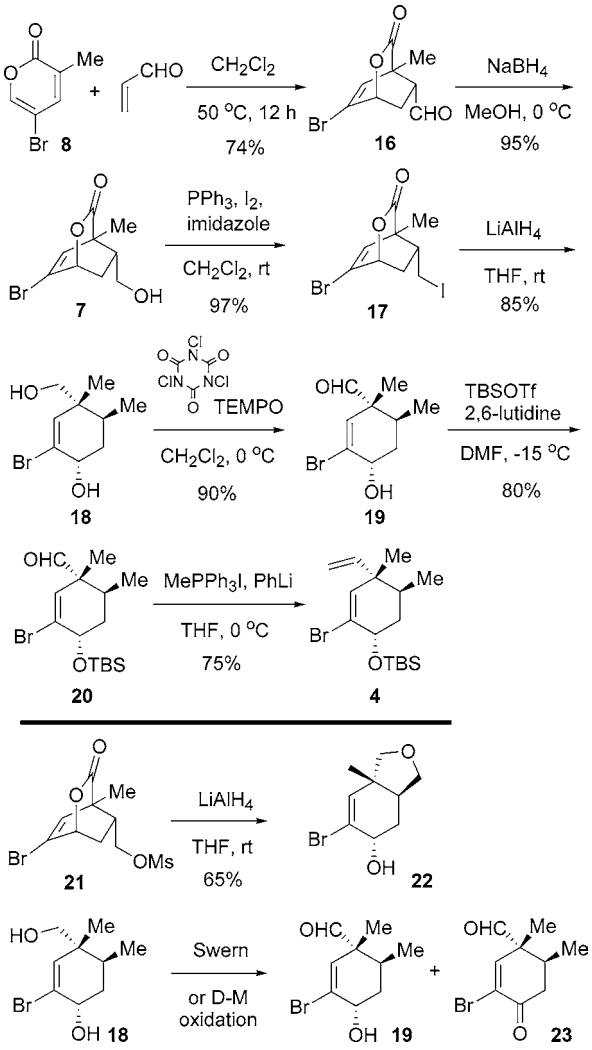
Scheme 4. Synthesis of Cyclohexene Core (±)-**4**



the bicyclolactones as a 9:1 mixture of the *endo*- and *exo*-isomer in 83% combined yield. Upon chromatographic separation, the *endo*-adduct **16** was reduced with $NaBH_4$ to furnish the alcohol **7** in 95% yield. Iodination with I_2/PPh_3 and subsequent treatment with excess $LiAlH_4$ reduced both lactone and primary iodide to afford alcohol **18** in 82% overall yield. When the mesylate **21** was used in lieu of **17**, the double reduction process resulted in formation of the tetrahydrofuran ring (**21** → **22**).

Despite our initial concern, the neopentyl primary alcohol of **18** was selectively oxidized into the aldehyde **19**, in the presence of the secondary hydroxyl group, when the trichlorocyanuric acid/TEMPO system was employed. Both Swern and Dess−Martin conditions were not as selective, providing a 2:1 (50% combined yield) and 4:1 (58% combined yield) mixture of desired aldehyde **19** and ketone **23**, respectively. TBS protection of the secondary hydroxyl group and subsequent Wittig olefination afforded cyclohexene core **4** in 31% total yield over seven steps from **8**.

In summary, the Pd-catalyzed coupling reaction of 3,5-dibromo-2-pyrone with Me_3Al−dimethylaminoethanol complex occurs regioselectively at C3 to provide 3-methyl-5-bromo-2-pyrone in high yield. A subsequent seven-step reaction sequence furnished cyclohexenyl bromide (±)-**4**, the key intermediate for the keto analogue of phomactin A, in 31% overall yield. Introduction of necessary chirality is being pursued at the D−A reaction stage and will be reported in due course.

Acknowledgment. Financial support was provided by the Korean Science and Technology Foundation (KOSEF, R01-2006-000-11283-0). K.R., Y.-S.C., and S.-I.J. thank the BK21 program for a fellowship.

Supporting Information Available: Details of experimental procedures and compound characterizations. This material is available free of charge via the Internet at http://pubs.acs.org.

OL061231Z

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