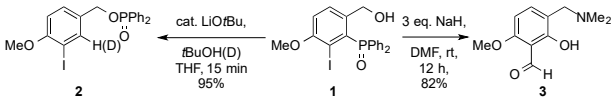
Generation of Benzyne Species from Diphenylphosphoryl Derivatives - Simultaneous Exchange of Three Functional Groups

Evgueni Gorobets, *Masood Parvez, Darren J. Derksen, and Brian A. Keay**[a]

Abstract: *Interaction of (2-diphenylphosphoryl-3-iodo-4-methoxy-phenyl) methanol with NaH in DMF at ambient temperature results in the generation of benzyne intermediates that can be trapped by furan or DMF. Trapping with DMF forms 3-(dimethylaminomethyl)-2-hydroxy-6-methoxy-benzaldehyde demonstrating the simultaneous exchange of three functionalities in a single step. The presence of the alkoxy substituent adjacent to iodine is critical for high regioselectivity addition of DMF. The corresponding bromide or triflate can be used in place of the iodide with equal efficiency. This methodology was used to synthesize the reported structure of gigasol and leading to a structural reassignment of this bis-coumarin natural product.*

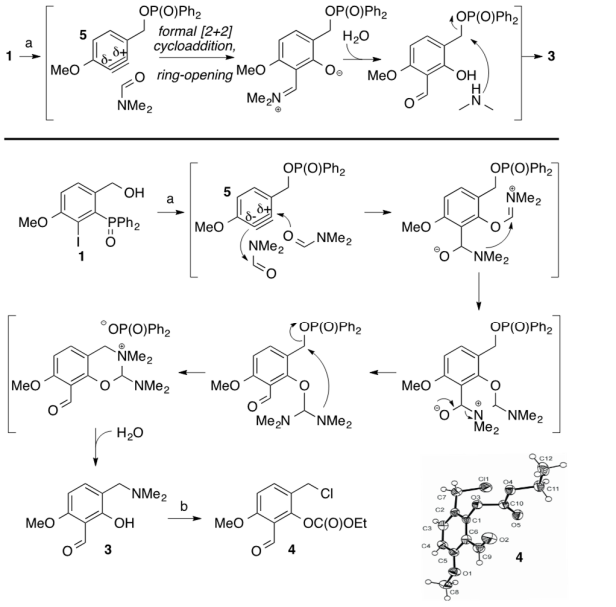
In our efforts toward making new derivatives of MeO-BIPHEP for asymmetric reactions[1-3] we encountered an unexpected result upon deprotonation of benzylic alcohol **1 (**Scheme 1). When **1** is exposed to LiO*t*Bu-*t*BuOH or other base metal alkoxides, migration of the diphenylphosphine oxide to the benzylic position occurs rapidly at room temperature (**2**). Exposure to NaH in DMF, results in the loss of diphenylphosphine oxide and the halogen, with the gain of an aldehyde and a tertiary amine (**3**). *We were intrigued by this reaction as it demonstrates the simultaneous exchange of three functional groups in a single step.* Although spectroscopic methods were informative in identifying the functional groups present in compound **3**, the relative arrangement of the substituents could not be determined unambiguously.



Scheme 1. Reactivity of benzyl alcohol **1** upon exposure to basic conditions.

In order to prepare material suitable for X-ray analysis, amorphous **3** was derivatized with EtOC(O)Cl yielding crystalline derivative **4** (Scheme 2). Based on the formation of **2**, we had anticipated that the aldehyde moiety would be *meta*- to the methoxy substituent but inspection of the crystal structure clearly revealed an aldehyde in the *ortho*- position. Although the addition of amides to benzynes is well established,[4-9] the observed product **3** would require either an equivalent of contaminating water to be contained in the reaction mixture or depend upon dimethylamine being liberated and recombining during aqueous workup (Scheme 2, Top). Given the reaction was completed with careful exclusion of water, on large scale and in the presence of excess sodium hydride, we offer an alternative mechanism incorporating 2 equivalents of DMF and intramolecular addition of dimethyl amine. Although unconventional, this alternative mechanism does not require contaminating water or high yielding intermolecular recombinations (Scheme 2, Bottom).

Scheme 2. Top: Formal [2+2] cycloaddition mechanism to yield **3**. Bottom: Proposed alternative mechanism for addition of DMF to benzyne intermediate



via intramolecular amine cyclization. (a) 3 eq. NaH, DMF, 12 h, rt, 82% (b) EtOC(O)Cl, NEt_3, DCM, 1.5 h, rt, 75%.

To support our mechanistic proposal, we performed a series of substrate-scope reactions (Table 1). To trap the intermediate benzyne directly, we added 10 eq. of furan and were pleased to observe the cycloaddition adduct in addition to **3** (53% combined yield). Upon exclusion of DMF from the reaction mixture and replacing with HMPA, the furan cycloaddition product can be obtained exclusively (44%). As our proposed mechanism suggests migration of the diphenylphosphine oxide to the benzyl oxygen, we anticipated that the phosphinate moiety would remain intact after the cycloaddition reaction with furan. Suspecting that the phosphinate may be cleaved in the reaction conditions or workup, we prepared a model *p*-methoxy benzyl phosphinate and observed cleavage in the reaction conditions (Table 1, entry 3). To understand the scope of leaving groups that could be used to generate the intermediate benzyne, Br and OTf analogs of **1** were subjected to the reaction conditions (Table 1, entries 5 and 7) with both yielding **3** as the major product with equal efficiency to the iodide. No reaction occurred with the Cl suggesting its leaving group ability is insufficient to generate the requisite benzyne. To explore whether an intramolecular cyclization from the phosphine

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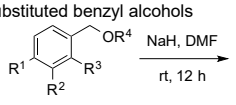
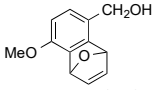
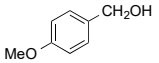
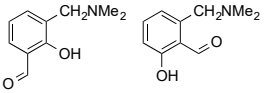
oxide may be the source of the newly formed phenolic oxygen, we prepared the analogous diphenylphosphine sulfide derivative of **1** (Table 1, entry 4) and subjected it to the standard reaction conditions in DMF. As the standard reaction product **3** was formed in high yield to the exclusion of any thiol-containing product, the migrating phosphine oxide does not appear to be the source of the phenol oxygen. The observed regioselectivity for formation of **3** is consistent with literature precedent for *o*-methoxy substituted benzynes.[10]

Table 1. Reactivity of substituted benzyl alcohols



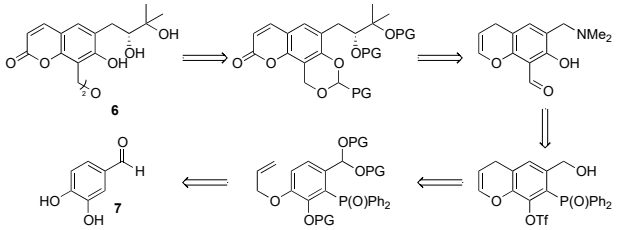
Entry	R^1	R^2	R^3	R^4	Product	Yield (%)
1[a]	OMe	I	$P(O)Ph_2$	H		53[b]
2[a,c]	OMe	I	$P(O)Ph_2$	H		44
3	OMe	H	H	$P(O)Ph_2$		77
4	OMe	OTf	$P(S)Ph_2$	H	**3**	83
5	OMe	Br	$P(O)Ph_2$	H	**3**	79
6	OMe	Cl	$P(O)Ph_2$	H	No reaction	--
7	OMe	OTf	$P(O)Ph_2$	H	**3**	84
8[d]	H	I	$P(O)Ph_2$	H		18

[a] addition of 10 eq. furan. *[b]* combined yield as 1:1 mixture with **3**. *[c]* HMPA used in place of DMF. *[d]* 1:1 mixture of regioisomers

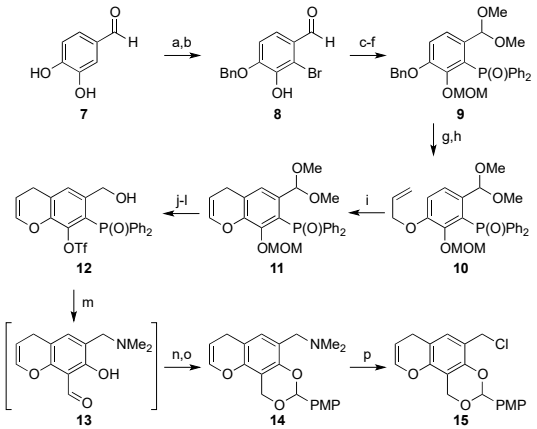
Since 1953 when J. D. Roberts[11] introduced the "at least transitory existence of an electrically neutral benzyne intermediate," the synthetic community has recognized arynes as extremely versatile building blocks. In the most recent and exhaustive review[12] over 75 individual natural products have been prepared using arynes as key synthetic intermediates. Recognizing that substitution of the methoxy substituent would allow access to coumarin natural products[13] we selected the reported structure of bis-coumarin natural product gigasol (**6**) as a synthetic target.[14] Gigasol was originally isolated from the aerial portion of *Angelica gigas*, a plant used in Korean folk medicine. Retrosynthetically, we envisioned **6** being derived from a late-stage dimerization, while introduction of the protected diol side chain could occur following the key step that simultaneously exchanges three functional groups in a single step (Scheme 3). Using other chemistry developed in our group, the precursor could be prepared using intermolecular nucleophilic addition of the allyloxy anion to a diphenylphosphinoyl-substituted aryl ring.[15] Following this approach, 3,4-dihydroxybenzaldehyde (**7**) would serve as a readily available starting material.

Chemoselective benzylation and regioselective halogenation converted **7** to **8** in 69% yield. Protection of the aldehyde and phenol positions was followed by introduction of the diphenylphosphine oxide produced **9** in 83% yield. Removal of the benzyl protecting group and formation of the benzopyran (**11**) proceeded smoothly. Notably, a modification of our previously published method[15] adding an equivalent of LiHMDS before adding LDA significantly improved yields from 35% up to 75%. A high yielding three step sequence of deprotection, triflate formation, and aldehyde reduction produced the key benzyne precursor (**12**). Exposure to NaH in DMF smoothly *exchanged three functional groups* on **12** yielding aminophenol **13,** that was then converted to the PMP acetal **14** after reduction of the aldehyde. Conversion to the unstable benzyl chloride (**15**) proceeds smoothly using well established conditions with methyl chloroformate and potassium carbonate.[16]

Scheme 3. Retrosynthesis of **6** (reported structure of gigasol[14])



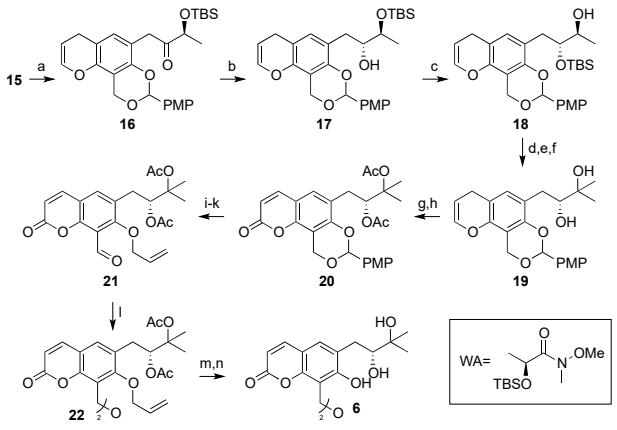
Scheme 4. Reagents and conditions: (a) BnCl, $NaHCO_3$, NaI (cat.), DMF, 40°C,



48 h; (b) Br_2, *t*-$BuNH_2$, toluene, -78°C to rt, 7 h, 69% over 2 steps; (c) MeOH, $(MeO)_3CH$, PTSA (cat.), reflux, 2 h; (d) MOMCl, NaOH, H_2O, DCM, Adogen 464, 0°C, 30 min; (e) *n*-BuLi, THF, -78°C, 0.5 h; PPh_2Cl, -78°C, 0.5 h, -78°C to rt, 2 h; (f) H_2O_2, MeOH, 0°C, 0.5 h, 83% over 4 steps; (g) 1,4-cyclohexadiene, Pd/C, EtOH, Et_3N (cat.), rt, 18 h; (h) allyl-Br, K_2CO_3, DMF, rt, 18 h, 95% over 2 steps; (i) LDA, THF, -78°C, 4 h; LiHMDS, -78°C, 0.5 h; I_2, -78°C, 15 min. 75%; (j) PTSA (cat.), acetone, rt, 3 h; (k) NaH, DMF, rt, 1 h; $PhNTf_2$, rt, 24 h; (l) DIBAL, THF, -78°C, 1 h, 88% over 3 steps; (m) NaH, DMF, rt, 4 h; (n) $NaBH_4$, EtOH, rt, 1 h; (o) *p*-$MeOC_6H_4CH(OMe)_2$, CSA (1.05 eq.), DCM, 0°C, 1 h, 56% over 3 steps; (p) MeOC(O)Cl, K_2CO_3, THF, -78°C to rt, 1 h, 88%.

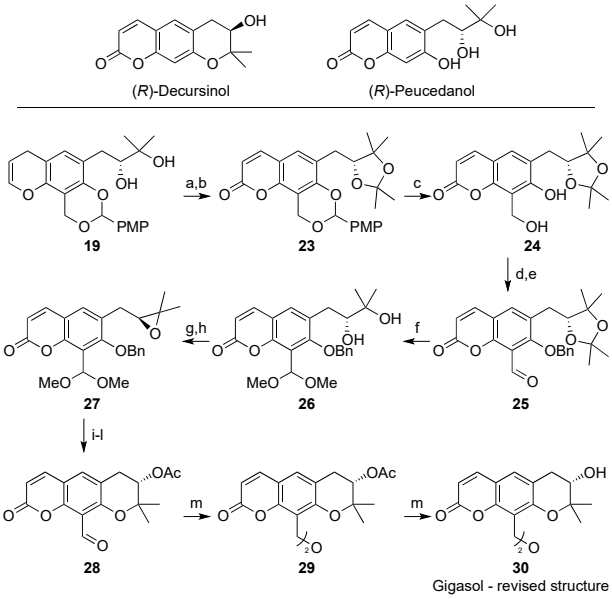
The benzylic chloride **15** was found to be very prone to decomposition in solution, particularly upon heating. To circumvent this challenge and activate the benzylic chloride for nucleophilic attack on the TBS-protected Weinreib amide of (*S*)-lactic acid, we selected a tellurium-mediated process[17] that yielded **16** in 84% yield (Scheme 5). Reduction of the ketone with $LiAlH(tBuO)_3$ (85:15 crude *dr*, separable), followed by base-induced migration of the TBS group to the internal hydroxyl. Given the modest steric differences between the two hydroxyls, only a slight excess of the desired TBS-protected alcohol could be acquired in a single reaction. As **17** and **18** are easily separable on silica gel, recovered starting material could be recycled through the process to push material to the desired **18**

(89% yield, 3 cycles). This was followed by Swern oxidation, TBS ether cleavage, and addition of MeLi to produce diol **19**. After protection to the corresponding diacetate (**20**), we investigated the chromene-coumarin transformation. Singlet oxygen oxidation with Rose Bengal as a sensitizer, followed by peroxide reduction with SMe_2 produced the corresponding lactol that was oxidized to the target coumarin **20** with manganese dioxide. Conversion to the requisite aldehyde **21** for dimerization was completed by acidic removal of the acetal, oxidation of the benzylic alcohol to the aldehyde, and finally allyl protection of the phenol. We were pleased to see that dimerization occurred upon addition of 1,1,3,3-tetramethyldisiloxane and catalytic TMSOTf.[18] Final deprotection then produced the reported structure of **6**.[14]



Scheme 5: (a) Te/*n*-BuLi, THF, 0ºC, 30 min; *n*-BuLi, -78ºC, 25 min; WA, -78ºC, 15 min, -78ºC to rt, 30 min, 84%; (b) LiAlH(O*t*-Bu)$_3$, DIGLIME, 0ºC, 12 h, rt, 1h, 75%; (c) K_2CO_3 (cat.), MeOH, rt, 20 h, 89%; (d) Swern oxidation; (e) TBAF, THF, 0ºC, 2 h; (f) MeLi, THF, -78ºC, 2 h, 75% over 3 steps; (g) Ac_2O, Et_3N, DMAP (cat.), DCM, rt, 44 h; (h) O_2 (air), Rose Bengal (cat.), EtOAc, irr, rt, 4 h; EtOAc, Me_2S, rt, 20 h; MnO_2, DCM, rt, 8 h, 72% over 2 steps; (i) 80 % AcOH, rt, 24 h; (j) MnO_2, DCM, rt, 2 h; (k) AllylBr, $NaHCO_3$, DMF, rt, 72 h, 66% over 3 steps; (l) TMDS, TMSOTf (cat.), toluene, -30ºC, 3 h; (m) K_2CO_3, MeOH, rt, 12 h; (n) Et_3SiH, $Pd(Ph_3P)_4$ (cat.), AcOH, DCM, rt, 2 h, 64% over 2 steps.

Unfortunately, comparison of our synthetic compound **6** did not match the reported literature values for gigasol.[14] Inspection of the data suggested that aliphatic side chain matched the *Decursinol* skeleton better than the *Peucedanol* framework found in **6** (Scheme 6). To test our proposal, we synthesized the revised target **30** to incorporate the *Peucedanol* aliphatic portion. From intermediate **19**, protection of the diol as an acetonide was followed by chromene-coumarin oxidation as previously described to produce **23**. Exposure of **23** to 70% acetic acid selectively cleaved the *p*-methoxyphenyl moiety while leaving the acetonide intact. Oxidation of the benzylic alcohol and benzyl protection of the phenolic position occurred under standard conditions to yield **25**. Treatment with PTSA in MeOH then cleaved the acetonide protection of the diol with concomitant dimethylacetal protection of the aldehyde forming **26**. Formation of epoxide **27** occurred with mesylation and corresponding inversion during nucleophilic displacement by the adjacent alcohol. In the course of forming the mesylate, a small amount of the bis-mesylate was formed that was suitably crystalline for x-ray analysis. With this information in hand, the configurations of the crystalline derivatives for both possible diastereomers of **17** were confirmed. Chemoselective transfer hydrogenation with 1,4-cyclohexadiene as a hydrogen source,[19] cyclization, and acetate protection produced aldehyde **28**. Dimerization to form the dimethyleneoxy bridge occurred as previously described in high yield followed by deprotection to yield target compound **30**. We were pleased to see that the ^{1}H-NMR spectrum of our revised target molecule **30** matched closely with the reported data for gigasol (<0.1 ppm deviation). Although the ^{13}C-NMR data of **30** and the literature data match well for most peaks (<0.4 ppm), resonances reported at 52.5 and 117.4 ppm differed from the observed peaks at 60.1 and 113.7 ppm in our synthetic compound.



Scheme 6: (a) $CH_3C(OCH_3)_2CH_3$, PPTS (cat.), DCM, rt, 30 min; (b) O_2 (air), Rose Bengal (cat.), EtOAc, irr, rt, 5 h; Me_2S, rt, 20 h; MnO_2, DCM, rt, 20 h; 72% over 2 steps; (c) 70 % AcOH, rt, 3 h, 81%; (d) MnO_2, DCM, rt, 20 h; (e) BnBr, K_2CO_3, DMF, rt, 44 h, 77% over 2 steps; (f) PTSA (cat.), MeOH, 50ºC, 44 h, 88%; (g) MsCl, Et_3N, DCM, 0ºC, 1h; (h) DBU, DCM, rt, 3 h, 67% over 2 steps; (i) 1,4-CHD, Pd/C, MeOH, rt, 2h; (j) PTSA (cat.), DCM, 0ºC, 30 min; (k) Ac_2O, Py, DMAP (cat.), DCM, rt, 1h; (l) 80 % AcOH, rt, 30 min, 61% over 4 steps; (m) TMDS, TMSOTf (cat.), toluene, -30ºC, 1h, 91%; (n) Et_3N, H_2O, MeOH, rt, 44 h, 89%.

In summary, we have reported a novel route to access benzyne derivatives under mild conditions. *The reactive benzyne intermediate can then be used to transpose three functional groups in a single step.* We have shown that this method can be used to access coumarin derivatives including the reported structure of gigasol. A revised structure and synthesis of gigasol that improves the match with literature data has also been reported.

Acknowledgements

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Keywords: benzyne • coumarin• Gigasol• Decursinol • Peucedanol

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