amides (entries 1,2), unavailable or formed in low yields by the direct cross-coupling route,[12] are obtained in good yields. Biaryl carbamates with the benefit of directed ortho metalation groups in the recipient aryl ring (entries 3,4) undergo the LDA-induced migration at room temperature. Extension to condensed biaryl (entry 5) and heterobiaryl (entries 6) synthesis is feasible. All biaryl amides are smoothly cyclized to the corresponding dibenzopyranones mainly without loss of TES substituent which may be removed (TBAF/THF/reflux or TFA/reflux) if desired. The benzo[*d*]naphtho[1,2-*b*]pyranone (entry 5) represents the ring system of ravidomycin and related classes of antitumor antibiotics of considerable current synthetic interest[13] while the azadibenzopyrone (entry 6) constitutes part skeleton of the chromone alkaloids.[14]

To demonstrate application, the synthesis of dengibsin (**15**), a fluorenone isolated from the Indian orchid *Dendrobium gibsonii*,[15] was undertaken. The 3-silyloxy carbamate **7**[16] was subjected to regiospecific metalation–bromination to give **8** which was smoothly cross coupled with boronic acid **9** under modified Suzuki conditions[3] to afford the biaryl **10**. A simple desilylation–isopropylation allowed the low-temperature ortho metalation–silylation sequence to give the key carbamate **11** which, upon exposure to LDA in refluxing THF, led to the carbamoyl migration product **12** in modest yield.[17,18] Methylation and C-desilylation proceeded unexceptionally to give the biary amide **13** which, upon treatment with LDA, underwent remote metalation–cyclization[3b] to provide the fluorenone **14**. Chemoselective deisopropylation[3b] furnished dengibsin **15**.[19] The conversion of other biary amides (Table I) to fluorenones by this general remote metalation protocol has been previously achieved in related systems.[3b]

In summary, a new general remote anionic Fries rearrangement has been uncovered and its broad utility for the regiospecific preparation of hindered biaryls and substituted dibenzo[*b*,*d*]pyranones[20] and fluorenones, including the natural product dengibsin, has been demonstrated. The retention of silyl substituents in the dibenzopyranones suggests exploration of potential regioselective ipso electrophilic and fluoride-mediated reactivity.[8] Consideration of the CIPE concept[2] coupled with advantages of synthetic connections to the adaptable directed ortho metalation[5] and cross-coupling[6] strategies promises future potential for effective and practical solutions in synthetic aromatic and heteroaromatic chemistry.[21,22]

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(16) Prepared in 90% yield from 3-methoxyphenyl dimethylcarbamate in two steps (BBr_3/CH_2Cl_2/−78 °C; TBDMSCl/imidazole).

(17) The 2′-deisopropylated product corresponding to **11** was also obtained (52%). The yield of **12** is based on the reconversion (*i*-PrI/K_2CO_3/Me_2CO, 98%) of this product into **11**.

(18) Attempts to use the Suzuki cross coupling for the direct preparation of derivatives related to **13** (without TES substituents) was uniformly unsuccessful, see: Fu, J.-m. Ph.D. Thesis, University of Waterloo, 1990 and ref 3b.

(19) Mp 234–235 °C (CH_2Cl_2) (lit.[15a] mp 227 °C), identical IR, MS, ^1H NMR with those reported.

(20) The recently announced[11] atrop-diastereoselective ring opening of dibenzopyranones related to entry 2 (Table I) by chiral nucleophiles anticipates considerable use of such systems for enantioselective biaryl synthesis.

(21) All new compounds show analytical and spectral (IR, NMR, MS) data consistent with the assigned structures.

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Pyruvate Aldolases as Reagents for Stereospecific Aldol Condensation

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Summary: KDPG aldolase, a representative member of the largest but as of yet unexplored group of aldolases which utilize pyruvate as the nucleophilic component in aldol condensation, accepts a number of unnatural aldehydes as electrophiles in stereospecific aldol condensation, providing access to highly and differentially functionalized α-keto acid products.

The aldolases have emerged as useful catalysts for stereocontrolled C–C bond formation in organic synthesis.[1,2] These enzymes can be categorized into three broad groups according to nucleophile type. The dihydroxyacetone phosphate aldolases have been investigated extensively as synthetic catalysts,[1-8] while a report on deoxyribose aldolase (DERA, EC 4.1.2.4), the only known aldolase which utilizes an aldehyde as the nucleophile, appeared only recently.[9] The remaining and largest group of aldolases, those which utilize pyruvate or phosphoenolpyruvate as the nucleophile, have yet to be investi-

Scheme I. KDPG Aldolase. Throughout "P" Represents PO_3H^-

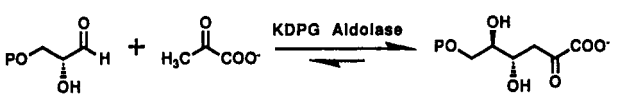

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Table I. Substrate Specificity of KDPG Aldolase

substrate	V_{rel}
nitropropanal	200
chloroacetaldehyde	120
glyceraldehyde	100
lactaldehyde	27
ribose-5-phosphate	5
erythrose	1.5
glycoaldehyde	1.5
benzaldehyde	0
butyraldehyde	0
ribose	0

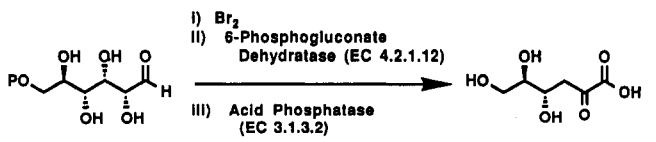
gated.[10] The highly and differentially functionalized products of the pyruvate aldolases make this group especially attractive as synthetic catalysts. The use of pyruvate aldolases has been hampered by early reports of very narrow substrate specificities.[14] We report here our initial studies of 2-keto-3-deoxy-6-phosphogluconate aldolase (KDPG aldolase, EC 4.1.2.14) which in vivo catalyzes the reversible condensation of pyruvate with glyceraldehyde 3-phosphate to form 2-keto-3-deoxy-6-phosphogluconate (Scheme I). The equilibrium constant lies in favor of synthesis ($K_{eq} \approx 1000\ M^{-1}$).[14] Our results show KDPG aldolase accepts unnatural electrophiles at synthetically useful rates and is a useful catalyst for organic synthesis.

KDPG aldolase was purified using a modified literature procedure.[15] The off-white powder prepared this way has a specific activity of 12 U/mg and is stable for at least 2 months at −85 °C. The enzyme showed virtually no loss of activity after stirring with pyruvate for 4 days, although during preparative-scale reactions the stability was less predictable: with some electrophiles all activity was lost in 15 h.

Ten aldehydes were tested as electrophiles. The rates of reaction are reported relative to D-glyceraldehyde (Table I), which is accepted at approximately 0.8% the rate of the natural substrate. All of the substrates are accepted at much lower rates than is the natural substrate: this pattern was also observed for DERA.[9] KDPG aldolase does not accept simple aliphatic aldehydes, in contrast to other aldolases. Benzaldehyde is not a substrate; this result is consistent with the substrate specificities of all other aldolases tested to date. Other than polar functionality at C2 or C3, there appears to be no general structural requirements for the electrophilic component.

To demonstrate the utility of KDPG aldolase in synthesis and to ensure aldol condensation proceeds stereospecifically with unnatural electrophiles, two substrates were utilized on a preparative scale. The ^1H and ^{13}C NMR spectra of both products are uninstructive in establishing the identity of the products. Both compounds can adopt several conformations including the δ-lactone, both the α- and β-furanose, and the open-chain form. 2-Keto-3-deoxygluconate (KDG) can also exist as α- and β-pyranoses and the γ-lactone. KDPG exists as an equal mixture of α- and β-furanoses and 9% of the open chain form.[16] The identity of KDG was therefore definitively established by comparison of the spectra and rotation to those of authentic KDG produced by dephosphorylation of KDPG, prepared from glucose-6-phosphate, with acid phosphatase (EC 3.1.3.2) (Scheme II). *These results demonstrate unambiguously that KDPG aldolase stereospecifically catalyzes the expected aldol condensation with unnatural electrophile substrates.*

Scheme II. Synthesis of KDG from Glucose-6-phosphate



2-Keto-3-deoxygluconate (KDG). To a solution containing sodium pyruvate (8.9 mmol), glyceraldehyde (8.9 mmol), and potassium phosphate (30 mM) in water (90 mL) at pH 7.5 was added KDPG aldolase (300 units) in a dialysis bag. The reaction was stirred for 2 days at which point the reaction had gone to 25% completion. The product was purified by anion exchange chromatography (formate, formic acid elution, 0–1 M linear gradient). The product-containing fractions were pooled, solvent was removed in vacuo, and the resulting clear oil was converted to the sodium salt. Removal of the solvent yielded 500 mg of a pale yellow oil. Spectral data (^1H, ^{13}C) and rotation were identical to authentic KDG.

D-Erythro-3,6-dideoxy-2-hexulosonate. To a solution of sodium pyruvate (7.5 mmol), D-lactaldehyde (7.5 mmol), and potassium phosphate (30 mM) in water (75 mL) at pH 7.5 was added KDPG aldolase (300 units) in dialysis tubing. After 2 days the reaction had gone to 30% completion and product was isolated by anion exchange chromatography as above to yield 380 mg of a bright yellow oil: $[\alpha]_D$ −9.4 (*c* 27.3, H_2O) (lit.[17] $[\alpha]_D$ −11.5 (*c* 7.32, H_2O) K^+ salt); ^1H NMR (300 MHz, D_2O) δ 0.9–1.2 (m, 3 H), 1.794 (dd, J_1 = 5.1 Hz, J_2 = 13.9 Hz, 0.3 H), 2.0–2.35 (m, 1.4 H), 2.450 (dd, J_1 = 7.4 Hz, J_2 = 13.9 Hz, 0.3 H), 3.45–4.05 (m, 2 H); ^{13}C NMR (75 MHz, D_2O, dioxane at 66.63) δ 13.81, 16.78, 17.16, 17.20, 17.84, 19.10, 19.13, 42.25, 43.12, 43.27, 66.79, 70.88, 75.68, 75.90, 81.69, 81.72, 82.91, 82.95, 95.76, 102.87, 102.99, 116.60, 176.65, 177.30.

We have established that KDPG aldolase accepts a variety of unnatural substrates at rates useful for preparative-scale synthesis. The enzyme-catalyzed reaction stereospecifically generates a new stereogenic center at C4. We are currently exploring other pyruvate aldolases for synthetic utility and methodologies for improving the rates of reaction of unnatural substrates.

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Supplementary Material Available: Enzyme isolation, substrate assay procedures, spectra and spectral data for KDG, and synthesis of KDG from glucose-6-phosphate (5 pages). Ordering information is given on any current masthead page.

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