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Total Synthesis of (±)-*O*-Methyl PD 116740

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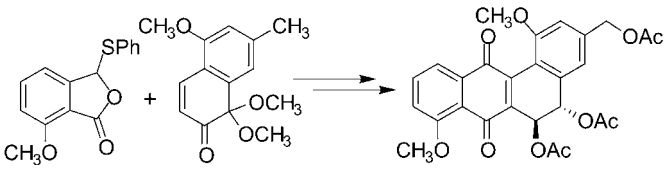
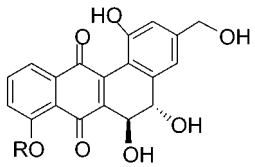
ABSTRACT



Condensation of the phthalide sulfide with an *ortho*-quinone monoketal was employed as a key step in the first total synthesis of a derivative of (±)-PD 116740.

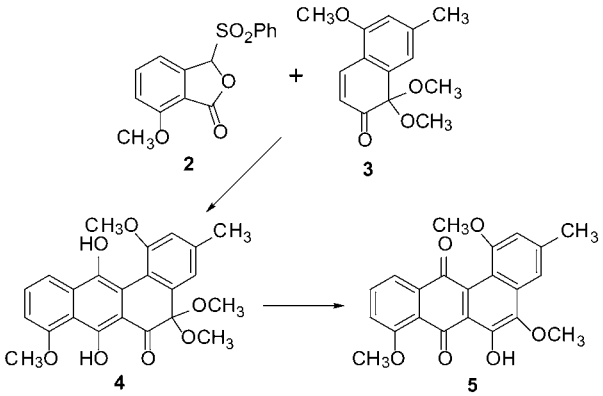
PD 116740[1] (**1a**) and TAN 1084[2] (**1b**) are the only angucyclines that have been isolated with 5,6-dihydroxylation. Since these, as well as other angucyclines, exhibit significant anticancer activity, there has been strong interest in their total synthesis.[3] To date, only two approaches to angucyclines with C5,C6-dihydroxylation have been reported, and both were model studies.[4,5]



1a R = CH_3
1b R = rhodinose

Our planned approach, shown in Scheme 1, was based on the expectation[6] that condensation of the phthalide sulfone

Scheme 1



2 with the *ortho*-quinone ketal **3** would provide an overall convergent route to the functionalized benz[*a*]anthracene **4**, with direct introduction of oxygenation at the C5 and C6 positions. There was a concern that the condensation would instead furnish **5**, through base-catalyzed elimination of methanol (vide supra).[5] Nevertheless, we were optimistic that we could overcome this anticipated difficulty.

The route that was employed to prepare the needed *ortho*-quinone ketal **3** is shown in Scheme 2 and exploits

(1) Wilton, J. H.; Cheny, D. C.; Hoakson, G. C.; Cun-heng, H.; Clardy, J. *J. Org. Chem.* **1985**, *50*, 3936.
(2) JP 009 263, 1990; JP 2 289 532, 1990; *Chem. Abstr.* **1991**, *115*, 47759n.
(3) For a review, see: Krohn, K.; Rohr, J. *Top. Curr. Chem.* **1997**, *188*, 127−195.
(4) Larsen, D. S.; O'Shea, M. D. *J. Org. Chem.* **1996**, *61*, 5681.
(5) Mal, D.; Roy, H. N.; Hazra, N. K.; Adhikari, S. *Tetrahedron*, **1997**, *53*, 2177.
(6) Hauser, F. M.; Rhee, R. P. *J. Org. Chem.* **1978**, *43*, 178. For use of this reaction in natural product syntheses, see: Hauser, F. M.; Mal, D. *J. Am. Chem. Soc.* **1984**, *106*, 1098. Hauser, F. M.; Prasanna, S. *Tetrahedron* **1984**, *40*, 4711. Hauser, F. M.; Chakrapani, S.; Ellenberger, W. P. *J. Org. Chem.* **1991**, *56*, 5248. Hauser, F. M.; Tommasi, R. A. *J. Org. Chem.* **1991**, *56*, 5758. Hauser, F. M.; Yin, H. *Org. Lett.* **2000**, *2*, 1045.

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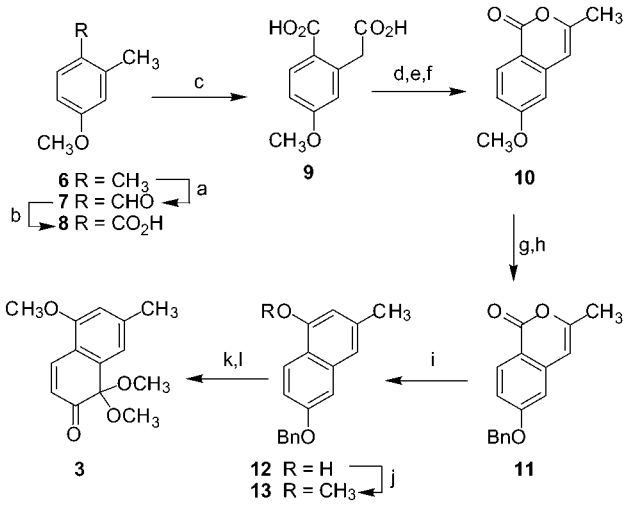
Scheme 2[a]



[a] Reagents and conditions: (a) $CuSO_4$, $K_2S_2O_8$, CH_3CN/H_2O. (b) $NaClO_2$, H_2NSO_3H, 2:1 H_2O/THF; 90% from **6**. (c) LDA, dimethyl carbonate, from −78 °C to rt; 86%. (d) py, Ac_2O, ether. (e) NaOH, Δ. (f) H^+, Ac_2O, EtOAc; 70% from **9**. (g) BBr_3, CH_2Cl_2, from −78 °C to rt, 24 h; 82%. (h) BnBr, K_2CO_3, acetone; 92%. (i) $CH_3P(O)(OCH_3)_2$, *n*-BuLi, THF, from −78 °C to rt. (j) $(CH_3O)_2SO_2$, K_2CO_3, acetone; 75% from **11**. (k) Pd/C, H_2, MeOH/EtOAc; 96%. (l) $PhI(OAc)_2$ (2.2 equiv), MeOH, from 0 °C to rt; 70%.

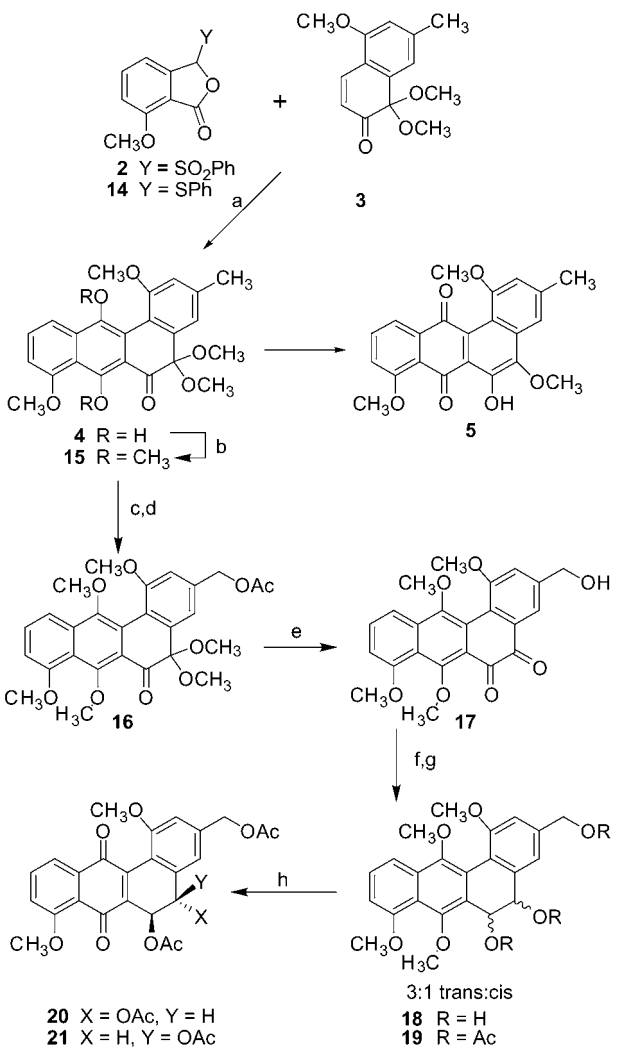
methodology previously developed by us for selective transformation of benzenoid systems and our development of a new procedure for regiospecific conversion of isobenzopyranones to 1-naphthols. A protocol we previously reported[7] was employed to regiospecifically convert the commercially available anisole **6** to the *ortho*-toluic acid **8**. Copper-catalyzed persulfate oxidation of the anisole **6** afforded the aldehyde **7**, which was oxidized with $NaClO_2$ to the acid **8**. Another procedure, also developed by us,[8] was used to convert the *ortho*-toluic acid **8** to the homophthalic acid **9**. Thus, treatment of **8** with 2 equiv of *n*-BuLi afforded the dianion intermediate, which was quenched with dimethyl carbonate. Subsequent workup resulted in in situ hydrolysis to the homophthalic acid **9** (86% yield). Sequential treatment of **9** with Ac_2O and pyridine, hydrolysis with decarboxylation, and then cyclization of the keto carboxylic acid intermediate with Ac_2O and catalytic $HClO_4$ afforded the benzopyranone **10** (70% overall yield).

At this point, it was necessary to prepare for eventual selective deprotection of the phenolic group and a change in protective groups was needed. Demethylation of **10** with BBr_3 followed by benzylation (BnBr and K_2CO_3) of the resultant phenol furnished the benzyl ether **11** (75% from **10**).

Although we have previously shown that benzopyranones can be converted to 1-hydroxy-2-carboxy-naphthoates through reaction either with the Reformatsky reagent derived from ethyl bromoacetate[9] or more conveniently with lithio-ethyl acetate,[10] we needed a method for regiospecific conversion of **11** to the unsubstituted naphthol **12**. Ultimately, we were able to accomplish this transformation in a regiospecific manner[11] through reaction of the anion of dimethyl methylphosphonate with the benzopyranone **11**.[12,13] The resultant naphthol **12** was methylated with K_2CO_3 and $(CH_3O)_2SO_2$ to afford the methyl ether **13** (75% from **11**). Hydrogenolysis of **13** followed by oxidation of the resultant phenol with $PhI(OAc)_2$ in MeOH[14] afforded the *ortho*-quinone ketal **3** (67% from **13**).

Attempted condensation of the anion of sulfone **2** with *ortho*-quinone ketal **3** failed to give any product (Scheme 3). It was unclear whether the reaction failure was due either to a steric effect from interaction of the phenyl-sulfonyl group in **2** and the methoxy group in **3** during the condensation or the possibility that the sulfone anion was insufficiently nucleophilic to add to the enone fragment in **3**. In an attempt

Scheme 3[a]



[a] Reagents and conditions: (a) *t*BuOLi, THF, −78 °C; 72%. (b) $(CH_3O)_2SO_2$, K_2CO_3, acetone; 91%. (c) NBS, CCl_4, hν, Δ; 48%. (d) NaOAc, DMF; 87%. (e) TFA, $CHCl_3/H_2O$; 92%. (f) $NaBH_4$, EtOH, from 0 °C to rt; 98%. (g) Ac_2O, Py, DMAP (cat.), CH_2Cl_2; 90%. (h) CAN, CH_3CN/H_2O, 0 °C; 74%.

(7) Hauser, F. M.; Ellenberger, S. R. *Synthesis* **1987**, 723.
(8) Hauser, F. M.; Rhee, R. P. *Synthesis* **1977**, 245.
(9) Hauser, F. M.; Rhee, R. P. *J. Am. Chem. Soc.* **1977**, *99*, 4533.

to evaluate these factors, reaction of the anion of the sulfide **14** with the *ortho*-quinone monoketal **3** was explored. Condensation of the anion of the sulfide **14** with **3** cleanly afforded a new product. The presence of only three methoxyl absorptions in the ^{1}H NMR spectrum and the presence of quinone absorptions in the IR spectrum established that the new product was not the desired hydroquinone **4** but was instead the quinone **5**. We suspected that **5** was formed from **4** during acid (HCl) neutralization of the reaction and did not arise through base-catalyzed elimination of methanol, as has been previously suggested.[5] This hypothesis was straightforwardly validated. When the reaction was quenched with acetic acid, exclusive formation of **4** was achieved in 72% yield. A further indication that **4** was stable to base was the fact that upon methylation with K_2CO_3 and $(CH_3O)_2SO_2$, the methyl ether **15** was exclusively produced in 91% yield.

Bromination of **15** with NBS afforded the bromomethyl intermediate (48%),[15] which was reacted with NaOAc in DMF to afford the acetoxymethyl compound **16** (87%). Brief treatment of **16** with TFA in $CHCl_3/H_2O$ gave the *ortho*-quinone **17** (98%). The excellent procedure reported by Harvey et al.,[16] for conversion of *ortho*-quinones to diols through reaction with $NaBH_4$ in the presence of air, was employed to convert **17** to a roughly 3:1 mixture of *trans*- and *cis*-diols **18** (98%). The diastereoisomeric mixture of diols **18** was only slightly soluble in most solvents. While it was possible to recrystallize the mixture from polar solvents, there did not seem to be significant separation of the isomers. In an effort to improve the solubility, the mixture was acetylated with Ac_2O and pyridine to afford **19**. Although we were now able to chromatograph the material, the isomers were still not cleanly separable by silica chromatography. Nevertheless, we were able to obtain a pure sample of the major product and establish through ^{1}H NMR spectroscopy that it was the *trans*-diacetate. The observed coupling constant for the H5 and H6 protons was 3.3 Hz, which is consistent with trans stereochemistry. Oxidation of **19** with CAN afforded the methyl ether acetate derivative **20** of PD 116740 and the cis isomer **21**, which were chromatographically separable.

In summary, we have accomplished the first total synthesis of a derivative of PD 116740. The developed route demonstrates that condensation of phthalide sulfides with *ortho*-quinone monoketals not only provides an expedient approach to benz[*a*]anthracene natural products but also results in direct introduction of 5,6-dihydroxylation. Furthermore, we have shown that benzopyranones can be regiospecifically converted to 1-naphthols through reaction with the anion of dimethyl methylphosphonate. We believe that this approach is generally applicable to other polycyclic aromatic natural products with this substitution pattern. In the following paper, we demonstrate its use to prepare an analogue of the benanomicin/pradimicin aglycone.

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(10) Hauser, F. M.; Pogany, S. *J. Heterocycl. Chem.* **1978**, *15*, 1535.
(11) Reaction of **11** with methyllithium, followed by intramolecular aldol reaction, gave regioisomeric naphthol products.
(12) This is a general reaction of benzopyranones, and this work will be published shortly.
(13) For the similar conversion of enol lactones to unsaturated enones see: Herrick, C. A.; Boehme, E.; Edwards, J. A.; Fried, J. H. *J. Am. Chem. Soc.* **1968**, *90*, 5926.
(14) Mallik, U.K.; Mallik, A. K. *Ind. J. Chem.* **1991**, *30B*, 611.
(15) The modest yield here is due to cleavage of the acetal by in situ-generated HBr. Undoubtedly, the yield could be improved by addition of a base.
(16) Zhang, J.; Dai, W.; Harvey, R. G. *J. Org. Chem.* **1998**, *63*, 8125.