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Regiospecific Synthesis of a Benanomicinone/Pradimicinone Analogue

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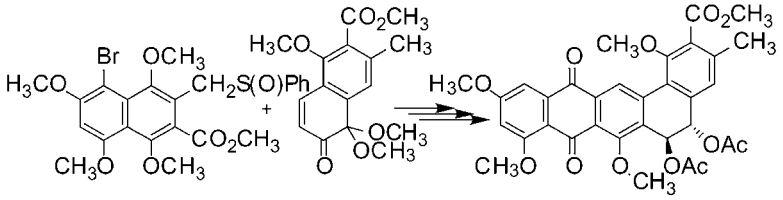
ABSTRACT



Condensation of a phenylsulfinyl naphthoate with an *ortho*-quinone monoketal has been used to accomplish a total synthesis of a benanomicinone/pradimicinone analogue.

In the preceding publication,[1] we established that condensation of a phthalide sulfide with an *ortho*-quinone monoketal provides a regiospecific and overall expedient route to PD116740, an angucycline with trans vicinal hydroxyl groups on the C5,C6-ethano bridge. In this paper, we describe an extension of this strategy to the synthesis of a benzo[*a*]-naphthacene-8,13-quinone with vicinal C5,C6-dihydroxylation. In accomplishing this work, we have performed a total synthesis of an analogue of the benanomicin/pradimicin aglycone.

Pradimicins[2] and benanomicins[3] (Figure 1) are potent antifungal antibiotics with potential therapeutic utility. These substances have as a core structural feature a benzo[*a*]-naphthacene-8,13-quinone ring system with trans vicinal hydroxyl groups at C5 and C6. Thus far, nineteen different pradimicins and benanomicins have been isolated. The structural diversity of these antibiotics is due to the presence of glycinyl, alanyl, and serinyl amino acids attached to the C2 carboxyl and the presence of a variety of mono- and disaccharides attached through the C5 hydroxyl group. Both pradimicins and benanomicins show excellent in vitro and in vivo activity against systemic fungal infections. In

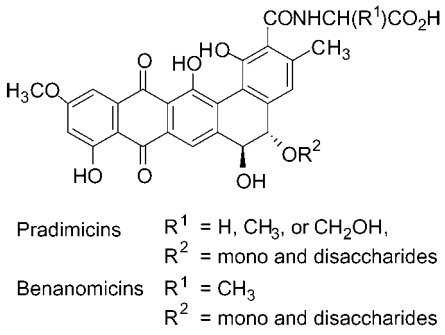


Figure 1.

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(2) Oki, T.; Konishi, M.; Tomatsu, K.; Tomita, K.; Saitoh, K.-I.; Tsunakawa, M.; Nishio, M.; Miyaki, T.; Kawaguchi, H. *J. Antibiot.* **1988**, *41*, 1701. Tsunakawa, M.; Nishio, M.; Ohkuma, H.; Tsuno, T.; Konishi, M.; Naito, T.; Oki, T.; Kawaguchi, H. *J. Org. Chem.* **1989**, *54*, 2532. Sawada, Y.; Nishio, M.; Yamamoto, H.; Hatori, M.; Miyaki, T.; Konishi, M.; Oki, T. *J. Antibiot.* **1990**, *43*, 771. Sawada, Y.; Hatori, M.; Yamamoto, H.; Nishio, M.; Miyaki, T.; Oki, T. *J. Antibiot.* **1990**, *43*, 1223. Saitoh, K.; Furumai, T.; Oki, T.; Nishida, F.; Harada, K.; Suzuki, M. *J. Antibiot.* **1995**, *48*, 162.

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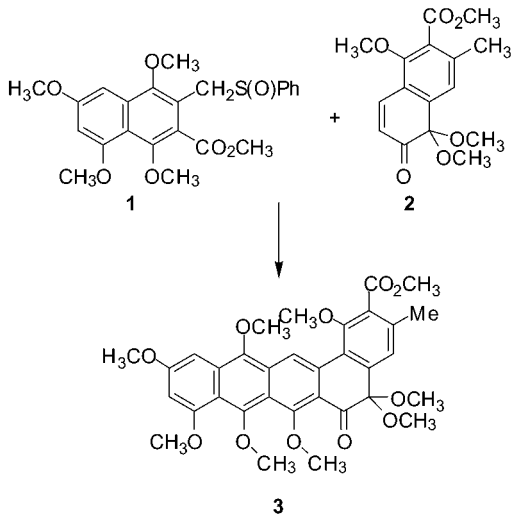
addition, benanomicins A and B inhibit de novo infection of human T-cells with HIV-1.[4]

While there has been strong interest in the total synthesis of benzo[*a*]naphthacene natural products,[5] there has been only one total synthesis of the pradimicin/benanomicin aglycone, which was performed by Suzuki et al.[6]

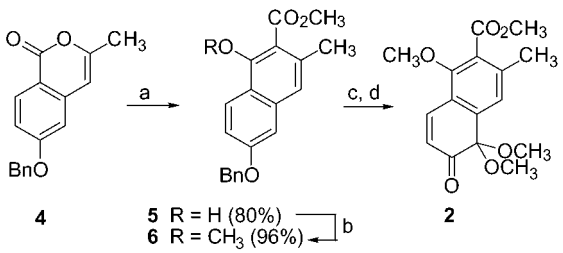
Our planned approach to the synthesis of the benzo[*a*]-naphthacene quinone ring system conceptually parallels that employed for synthesis of PD116740, in that the angular ring system would be regiospecifically fabricated through use of the *ortho*-quinone monoketal **2** in a condensation reaction (Scheme 1).[1] In this case, we would condense an *ortho*-phenylsulfinylmethyl naphthoate with **2**. This condensation reaction was previously developed and used by us for regiospecific construction of naturally occurring polycyclic aromatic systems.[7]

Scheme 1



Preparation of the needed *ortho*-quinone monoketal **2** capitalized on our earlier development of a route to the benzyl ether-protected isobenzopyranone **4** (Scheme 2).[1] We have previously shown that reaction of isobenzopyranones with the lithium enolate of ethyl acetate regiospecifically affords 1-hydroxy-2-carboxynaphthoates in high yield.[8] The corresponding reaction of **4** with the lithium enolate of methyl acetate afforded the naphthoate **5** in 80% yield. The resultant naphthol **5** was methylated with K_2CO_3 and $(CH_3O)_2SO_2$ to the methyl ether **6** (96%). Sequential hydrogenolysis of **6** followed by oxidation of the resultant phenol with $PhI(OAc)_2$ in MeOH[9] afforded the *ortho*-quinone ketal **2** (68% from **6**).

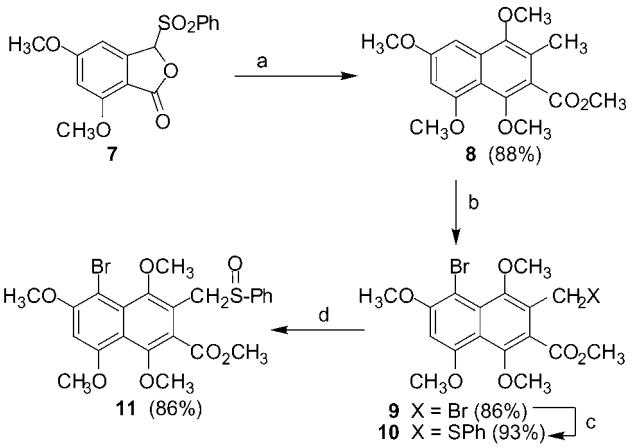
Scheme 2[a]



[a] Reagents and conditions: (a) LDA/THF, $CH_3CO_2CH_3$ (80%). (b) $(CH_3O)_2SO_2$, acetone, K_2CO_3 (96%). (c) H_2/Pd−C, MeOH (98%). (d) $PhI(OAc)_2$, CH_3OH (68%).

Preparation of the *ortho*-phenylsulfinyl naphthoate **11** was accomplished as shown in Scheme 3. Condensation of the anion of the sulfone **7** with methyl crotonate afforded the 1,4-dihydroxynaphthoate intermediate, which proved to be too reactive for isolation, readily undergoing air oxidation to the quinone. To overcome this problem, the initially formed naphthoate dianion was directly treated with $(CH_3O)_2SO_2$ in the same flask in which the condensation was conducted. This protocol produced a regioisomeric mixture of mono- and dimethylated products. The mixture was isolated and subjected to additional methylation, affording the dimethyl ether **8** in 88% overall yield from **7**.

Scheme 3[a]



[a] Reagents and conditions: (a) (i) LiO*t*Bu, THF, methyl crotonate; (ii) $(CH_3O)_2SO_2$, K_2CO_3, acetone (88% for two steps). (b) NBS, CCl_4 (86%). (c) KOH, PhSH, MeOH (93%). (d) $NaBO_3 \cdot 4H_2O$, AcOH (86%).

Attempted free-radical bromination of the methyl group in **8** with 1 equiv of NBS afforded a mixture of methyl and ring brominated products, as well as unreacted starting material. Bromination with 2 equiv cleanly afforded the dibrominated product **9** in 86% yield. Since we expected to

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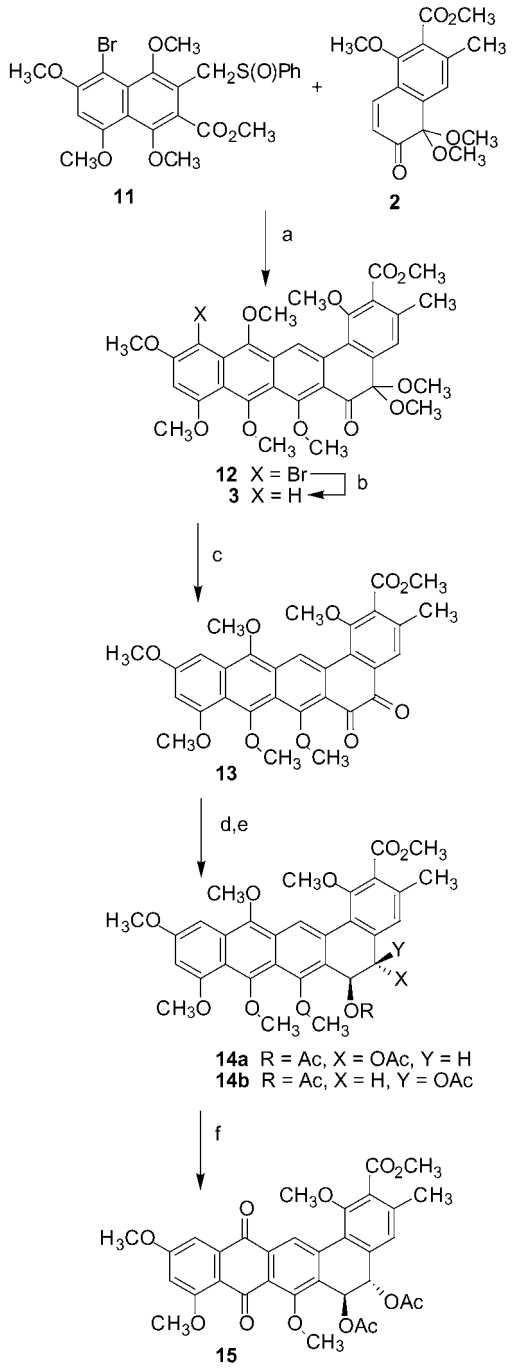
Scheme 4[a]



[a] Reagents and conditions: (a) (i) *t*BuOLi, THF/DMSO; (ii) $(CH_3O)_2SO_2$, acetone, K_2CO_3 (31% for two steps). (b) Pd/C, H_2 (97%). (c) TFA, $H_2O/CHCl_3$. (d) $NaBH_4$, EtOH. (e) Ac_2O, Py, DMAP (cat.) (85% for three steps). (f) CAN, H_2O/CH_3CN (44%).

be able to remove the aryl bromine at a subsequent stage in the synthesis (vide supra), formation of this product was not a serious concern. Reaction of **9** with thiophenoxide afforded the thiophenyl methyl compound **10** in 93% yield, and this was readily oxidized with peroxyboric acid to the sulfoxide **11** in 86% yield.

Condensation of the anion of the sulfoxide **11** with the *ortho*-quinone monoketal **2** proved to be challenging (Scheme 4). In THF, none of the desired product was formed. However, when DMSO was employed as a cosolvent, **12** was isolated, following methylation, in 31% yield. Hydrogenation of **12** resulted in reductive replacement of the aryl bromine, affording **3** in 97% yield.

Preparation of the *ortho*-quinone **13** via hydrolysis of the ketal in **3** initially proved to be experimentally challenging. When the hydrolysis was run for 5 min, only TLC baseline material was produced. After some experimentation, it was found that shorter, not longer, reaction times were required to produce the product. Ultimately, we found that hydrolysis of **3** for less than 15 s cleanly afforded the quinone **13**. Although analysis of a TLC indicated that the material was pure, when silica chromatography was attempted, substantial loss of the material occurred. Ultimately, we elected not to purify the quinone **13** but instead sequentially treated it with $NaBH_4$ in the presence of air[10] and then acetylated (Ac_2O and pyridine) the resultant diol product. This afforded a diastereoisomeric mixture of *trans*- and *cis*-diacetates **14a** and **14b** in 85% overall yield from **3**. The diastereoisomer diacetates, formed in a 3:1 ratio, were separated by silica chromatography. The major product was shown to be the trans isomer **14a**, as evidenced by the 3.0 Hz coupling constant for the H5 and H6 protons in the ^1H NMR spectrum. Oxidation of **14a** with $Ce(NH_4)_2(NO_3)_6$ in acetonitrile/water afforded the expected quinone **15**.

In summary, we have shown that the use of a sulfinylmethyl naphthoate condensation with an *ortho*-quinone monoketal can be used to prepare benzo[*a*]naphthacene quinones with direct introduction of C5,C6-dihydroxylation. Use of this strategy for the preparation of other naturally occurring quinone systems with C5,C6-dihydroxylation is under investigation.

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