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Synthesis of (+)-puraquinonic acid

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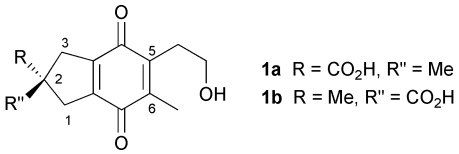
(+)-Puraquinonic acid (1a) was synthesized, using a route based on ring-closing metathesis and radical cyclization, the chirality of the quaternary carbon being controlled by a temporary adjacent asymmetric center.

Puraquinonic acid (**1b**), shown in the present work to have most probably the 2*R*-configuration, is a fungal metabolite[1,2] that induces differentiation in HL-60 cells.[1] This property is relevant to the design of antileukemia drugs.[3] The absolute configuration of natural **1** was previously unknown, and recent publications from this laboratory[4,5] describe syntheses of the racemic compound. Making optically active **1** is a more demanding task because the features responsible for its chirality are far removed from C(2).[6]



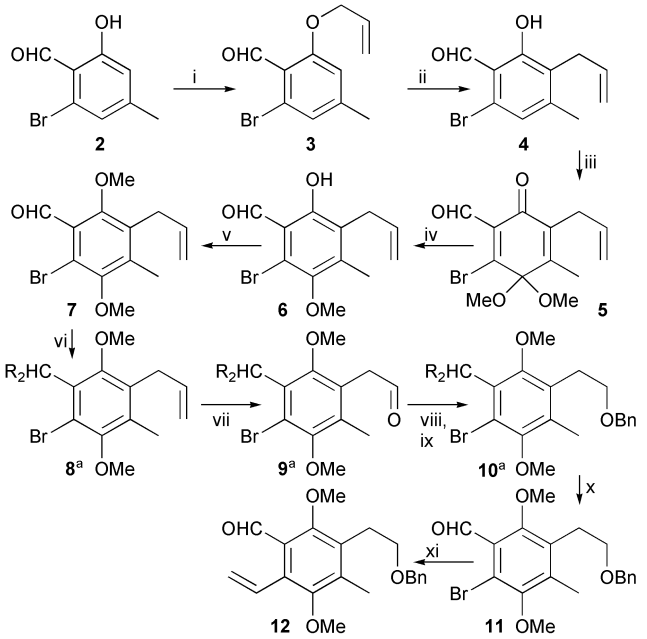
1a R = CO_2H, R'' = Me
1b R = Me, R'' = CO_2H

Our approach is based on the use of a temporary asymmetric center at C(3) (see **19**, Scheme 2), and on the fact that radical cyclization of the derived Stork bromo acetals[7] **20** must give a *cis*-fused[7b,8] product (**20** → **21**), thereby forming the quaternary center at C(2) with a configuration determined by that of the starting alcohol **19**.

O-Allylation of phenolic aldehyde **2**[9–12] (**2** →**3**, NaH, allyl bromide, 79%) and thermal Claisen rearrangement (decalin, 200 °C, 66%) gave **4**. Introduction of a second oxygen (see **6**) was initially troublesome, until we found that sequential oxidation to a quinone ketal[13] [**4** → **5**, $PhI(OAc)_2$, MeOH, 83%], Zn-mediated reduction[14] (**5** → **6**, Zn–AcOH, 70%), and methylation (MeI, K_2CO_3, 92%) gave the requisite *p*-dimethoxy compound **7** (Scheme 1). The aldehyde was protected as its dimethyl acetal [$(MeO)_3CH$, $TsOH.H_2O$, 4 Å sieves, 97%)], and the side chain olefin was degraded (**8** → **10**) by double bond cleavage (OsO_4, $NaIO_4$, 95%), reduction ($NaBH_4$, MeOH, 95%), and benzylation (NaH, Bu_4NI, THF, BnBr, 92%). Acetal hydrolysis (**10** → **11**, Amberlite IR-120, aqueous acetone, 95%) and Stille coupling with tributylvinyltin [CuI, $Pd(PPh_3)_4$, 66%] gave the key intermediate **12**.

Asymmetric aldol condensation[15] of **12** with (*S*)-4-isopropyl-3-propionyl-2-oxazolidinone, using $Bu_2BOSO_2CF_3$ to generate the intermediate enol, gave **13** (78%) (Scheme 2), whose stereochemistry we assign on the basis of precedent,[15,16] the coupling constant for the C(1′)**H** (J = 9.3 Hz) indicating[16a] an *anti* relationship for the substituents at C(1′) and C(2′). This is an uncommon stereochemical outcome, but one for which there is precedent with aromatic aldehydes.[16a] The hydroxy was silylated (*t*-$BuMe_2SiOSO_2CF_3$, 2,6-lutidine, 95%) and the chiral auxiliary was replaced by a benzyloxy group (BnOLi,[17] THF, 89%) (**13** → **14**). Reduction (DIBAL-H, 89%) then afforded primary alcohol **15**. Replacement of the hydroxy by an *o*-nitrophenylseleno group (**15** → **16**, *o*-$(NO_2)C_6H_4SeCN$, Bu_3P),[18] and selenoxide elimination (30% H_2O_2, 81% from **15**) served to generate a double bond (**15** → **16** → **17**) and set the stage for a ring-closing metathesis that would form the five-membered ring of puraquinonic acid. Treatment of **17** with Bu_4NF in THF effected desilylation (**17** → **18**, 95%), and heating with tricyclohexylphosphine[1,3-bis(2,4,6-trimethylphenyl)-4,5-dihydroimidazol-2-ylidene][benzylidene]ruthenium(IV) dichloride[19] in CH_2Cl_2 gave the optically active allylic alcohol **19** in 88% yield.† Examination of the alcohol by HPLC [CHIRALPACK AS, hexane] and comparison with a racemic sample showed that **19** had ee > 98%. The alcohol was readily converted into the Stork bromo acetals (**19**→ **20**, ethyl vinyl ether, Br_2, 2,6-lutidine, 91%), and these underwent radical cyclization when treated with Bu_3SnH and AIBN in refluxing PhMe. Best results (85% yield) were obtained when the stannane and initiator were added in one portion. The cyclization must occur with *cis* ring fusion,[7b,8] and so the stereochemistry of **21** is assigned as shown.

The tetrahydrofuran ring was now degraded to remove the C(3) oxygen (see **21**) and generate the carboxy at C(2). Acid hydrolysis (1:4 AcOH–water, 91%) gave lactols **22**, and mesylation (MsCl, Et_3N, THF, 75%) afforded the sensitive elimination product **23**, which should be used immediately. Selective cleavage of the vinyl ether double bond was best done with the OsO_4–$NaIO_4$ combination, rather than with O_3, and gave **24**. Oxidation of the CHO group ($NaClO_2$, NaH_2PO_4, 2-methyl-2-butene), titration with CH_2N_2 and treatment of the



Scheme 1 [a]R = OMe. *Reagents and conditions*: (i) NaH, allyl bromide, DMF, 2 h, 79%; (ii) degassed *trans*-decalin, reflux, 7 h, 66%; (iii) $PhI(OAc)_2$, MeOH, 12 h, 83%; (iv) Zn powder, AcOH, 7 h, 70%; (v) MeI, K_2CO_3, DMF, 12 h, 92%; (vi) $(MeO)_3CH$, $TsOH{\cdot}H_2O$, MeOH, reflux, 12 h, 97%; (vii) OsO_4 (catalytic), $NaIO_4$, 5:2:2 CCl_4–water–*t*-BuOH, 1.5 h, 95%; (viii) $NaBH_4$, MeOH, 0 °C, 1.5 h, 95%; (ix) NaH, BnBr, THF, 12 h, 92%; (x) 1:1 acetone–water, Amberlite IR-120, 12 h, 95%; (xi) $Bu_3(CH_2{=}CH)Sn$, CuI, $Pd(PPh_3)_4$, PhMe, reflux, 40 h, 66%.

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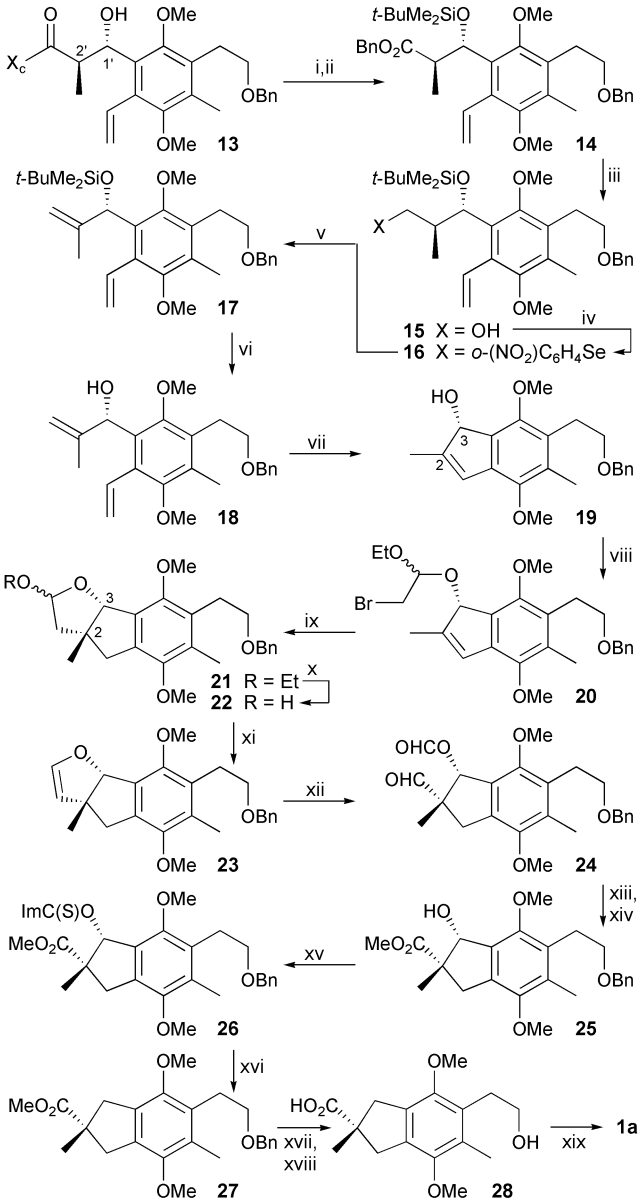
crude product with methanolic K_2CO_3 [to hydrolyze the C(3) formate] afforded hydroxy ester **25** (54% overall from **23**). The C(3) hydroxy was now removed by Barton–McCombie deoxygenation[5,20] (**25** → **26**, Im_2CS, DMAP, *ca*. 96%; **26** → **27**, Bu_3SnH, AIBN, PhMe, 73–77%). Hydrogenolysis (H_2, Pd/C, 96%) released the sidechain hydroxy and the ester was hydrolyzed with LiOH ($LiOH{\cdot}H_2O$, dioxane, water, 95%). Finally, treatment with $Ce(NH_4)_2(NO_3)_6$ in the presence of 2,6-pyridinedicarboxylic acid *N*-oxide[4,21] gave synthetic puraquinonic acid (81%) with $[\alpha]_D^{22}$ +3.2° (*c* 0.3 $CHCl_3$), $[\alpha]_D^{22}$ +3.1° (*c* 0.7 CH_2Cl_2). The natural product is reported[1] to have



Scheme 2 *Reagents and conditions*: (i) *t*-$BuMe_2SiOSO_2CF_3$, 2,6-lutidine, CH_2Cl_2, 1 h, 95%; (ii) BnOLi, THF, 0 °C, 6 h, 89%; (iii) DIBAL-H, CH_2Cl_2, 0 °C, 1 h, 89%; (iv) *o*-$(NO_2)C_6H_4SeCN$, Bu_3P, THF, 12 h; (v) 30% H_2O_2, THF, 5 h, 81% from **15**; (vi) Bu_4NF, THF, 36 h, 95%; (vii) tricyclohexylphosphine[1,3-bis(2,4,6-trimethylphenyl)-4,5-dihydroimidazol-2-ylidene][benzylidene]ruthenium(IV) dichloride, CH_2Cl_2, reflux, 20 h, 88%; (viii) ethyl vinyl ether, Br_2, CH_2Cl_2, 2,6-lutidine, 20 h, 91%; (ix) Bu_3SnH and AIBN (both added in one portion), PhMe, reflux, 1.5 h, 85%; (x) 1:4 AcOH–water, THF, reflux, 12 h, 91%; (xi) MsCl, Et_3N, THF, 2 h, then reflux, 1 h, 75%; (xii) OsO_4 (catalytic), $NaIO_4$, 5:2:2 CCl_4–water–*t*-BuOH, 9 h; (xiii) $NaClO_2$, 2-methyl-2-butene, NaH_2PO_4, *t*-BuOH, 3 h; (xiv) CH_2N_2, Et_2O, then MeOH, K_2CO_3, 54% from **23**; (xv) Im_2CS, DMAP, CH_2Cl_2, reflux, 19 h, *ca*. 96%; (xvi) Bu_3SnH, AIBN, PhMe, reflux, 1.5 h, 73–77%; (xvii) H_2 (balloon), Pd/C, MeOH, 30 min, 96%; (xviii) $LiOH{\cdot}H_2O$, 1:1 dioxane–water, 3 h, 95%; (xix) $Ce(NH_4)_2(NO_3)_6$, 2,6-pyridinedicarboxylic acid *N*-oxide, 2:1 MeCN–water, 5 h, 81%.

$[\alpha]_D^{22}$ + 1° (*c* 1.0 $CHCl_3$), but HPLC comparison [CHIRACEL OD-RH, 1:1 *i*-PrOH–water] showed that the natural and synthetic compounds are enantiomeric, and remeasurement of the specific rotation of the natural material gave $[\alpha]_D^{22}$ −2.2° (*c* 0.55 $CHCl_3$), $[\alpha]_D^{22}$ −1.3° (*c* 0.6 CH_2Cl_2). Therefore, natural (−)-puraquinonic acid has the 2*R* configuration, based on our stereochemical assignment to C(1′) in **13**.

All new compounds were characterized spectroscopically except for **16**, **24** and **26**, which were used crude.

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Notes and references

† Ring-closing metathesis did not work with **17**.

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