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Model studies towards the challenging angularly-oxygenated core of several angucyclinones from an oxidative dearomatization strategy†

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Up to six differently substituted highly challenging angularly-oxygenated tricyclic core models of natural angucyclinones were stereoselectively synthesized from a common *p*-quinol intermediate obtained from Oxone-mediated oxidative dearomatization of the corresponding tricyclic phenol.

Angucyclines and angucyclinones, a large group of aromatic polyketide secondary metabolites, constitute an important family of microbial antibiotics, isolated from various members of the bacterial genus *Streptomyces*, exhibiting a broad spectrum of biological properties including antiviral, antifungal, antitumor, and enzyme inhibitor activity.[1] Most of these antibiotics are structurally characterized by their benz[*a*]anthraquinone ABCD angular tetracyclic skeleton (Fig. 1) sharing a methyl group at C-3 and oxygen functionalities at C-1 and C-8, with varying degree of unsaturation and oxygenation. These fascinating structural features as well as their diverse range of biological activities have provided organic chemists with attractive targets for the development of various synthetic methodologies.[1,2]

Of particular importance are derivatives bearing one or two hydroxyl groups located at the angular 4a and 12b positions connecting the rings A and B (Fig. 1). While the stereocontrolled assembly of the members of the SF 2315-type, bearing an oxygen function at C-4a, has been achieved using a Diels–Alder reaction[3] or a biomimetic approach,[4] the synthesis of angucyclinones with one hydroxyl group at C-12b (azicemycin-type) and specially those bearing two oxygenated substituents at the AB ring junction (aquayamycin-type) has been much less explored and remains a challenge for synthetic organic chemists.[5] To the best of our knowledge, only three very particular and limited model studies of this subclass of angucyclinones have been reported,[6–8] together with two total syntheses: the racemic 8-deoxy analogue of WP 3688-2 (**1** in Scheme 1) by Krohn,[9] and aquayamycin (**2** in Scheme 1) by Suzuki.[10] In addition to this synthetic effort, new and general routes to the angularly-oxygenated core of this type of angucyclinones are welcome.

We have recently reported a practical method for the simple and selective oxidative dearomatization of differently substituted *p*-alkyl phenols into *p*-peroxy quinols and *p*-quinols using Oxone® in the presence of $NaHCO_3$, as a source of singlet oxygen.[11] Herein, we describe a direct and stereocontrolled access to six differently

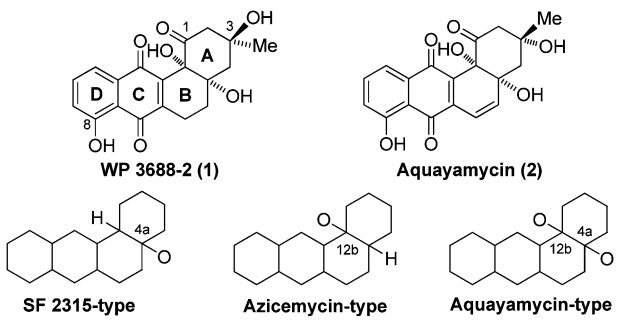
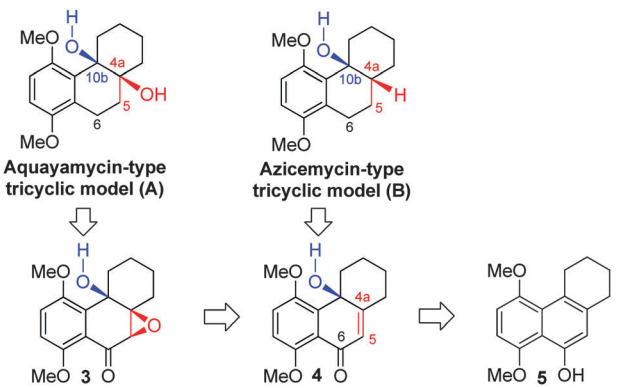


Fig. 1 Diverse structure of angucyclinones and types of derivatives with angular oxygens at 4a and/or 12b positions.



Scheme 1 Retrosynthesis towards tricyclic angularly-oxygenated core models of angucyclinones.

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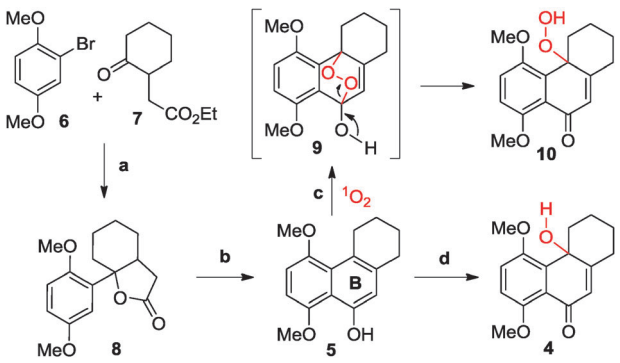
substituted angularly-oxygenated tricyclic core models of natural angucyclinones from a common *p*-quinol intermediate obtained from Oxone-mediated oxidative dearomatization of the corresponding tricyclic phenol. We envisaged tricyclic structures **A** and **B**, shown in Scheme 1, as convenient angularly-oxygenated core models of aquayamycin-type and azicemycin-type angucyclinones, respectively, to validate our oxidative dearomatization approach.

As can be seen in retrosynthetic Scheme 1, the angular tertiary benzylic OH at C-10b present in both types of tricyclic models (C-12b in tetracyclic angucyclinones) could come from the corresponding *p*-quinol intermediate **4**, formed from tricyclic phenol **5** after oxidative dearomatization. On the other hand, epoxide **3** would give rise to the second angular oxygenated substituent at C-4a present in the aquayamycin-type derivatives.

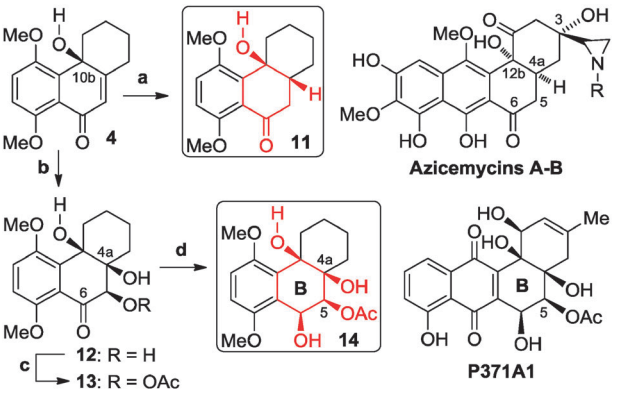
Tricyclic phenol **5** was obtained in two steps from commercially available substrates **6** and **7** (Scheme 2). Thus, the reaction of the Grignard reagent obtained from 2-bromo-1,4-dimethoxy benzene (**6**) with ketone **7** afforded lactone **8** in 87% yield. The Friedel–Crafts acylation of compound **8** with PPA was followed by the aromatization of the B ring, leading to tricyclic phenol **5**, in 79% yield. The Oxone treatment of tetrahydrophenanthrol **5** under our oxidative dearomatization conditions[11] gave rise, after [4+2] cycloaddition of the singlet oxygen generated, to the endoperoxide intermediate **9**, which evolved to the corresponding *p*-peroxyquinol **10**, isolated in 44% yield after flash chromatography (Scheme 2). When the same reaction was followed by the addition of a reducing agent such as $Na_2S_2O_3$, *p*-quinol **4** was obtained in 52% yield.

With *p*-quinol **4** in hand, we carried out the first approach to synthesise one of the angularly-oxygenated core of natural angucyclinones, the azicemycin-type tricyclic model (**B** in Scheme 1). Azicemycins A and B (Scheme 3) were isolated from *Kibdelosporangium* sp. MJ126-NF4 and have antimicrobial activity against Gram positive bacteria.[12] They have a unique aziridine moiety[13] at C-3 and, in the B ring, angular OH at C-12b, saturated C4a–C5 bond and carbonyl group at C-6. The access to the tricyclic model of azicemycins (**11** in Scheme 3) was possible after stereoselective hydrogenation of *p*-quinol **4** in the presence of 10% Pd–C and 25% aq. $NaNO_2$,[14] in 78% yield.

Our next synthetic goal was an aquayamycin-type tricyclic model (**A** in Scheme 1) such as derivative **14** (Scheme 3), whose all-*cis* tetraoxygenated B ring is present in the structure of angucyclinone P371A1. This natural product was isolated from



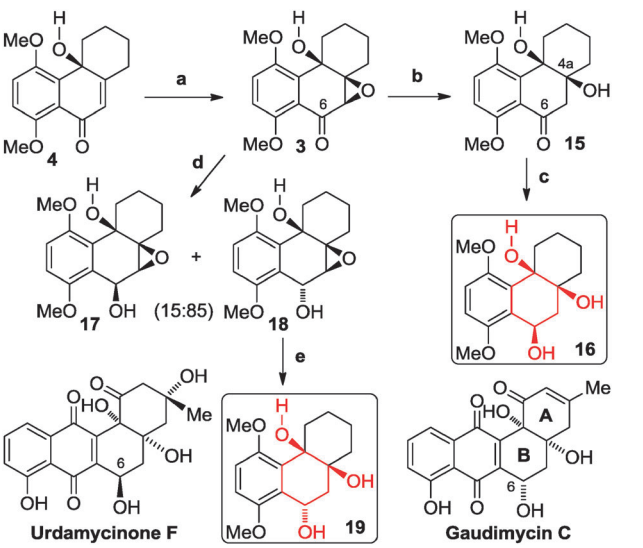
Scheme 2 Synthesis of **10** and **4**: (a) i. **6**, Mg, THF, reflux, 2 h; ii. **7**, THF, rt, 2 h, 87%; (b) PPA, 90 °C, 2 h, 79%; (c) Oxone, $NaHCO_3$, CH_3CN–H_2O, rt, 2 h, 44%; (d) i. Oxone, $NaHCO_3$, CH_3CN–H_2O, rt, 2 h; ii. $Na_2S_2O_3$, rt, 2 h, 52% for the two steps.



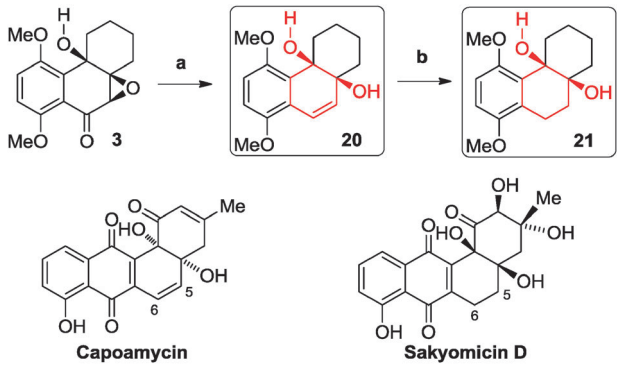
Scheme 3 Synthesis of tricyclic models **11** and **14** from *p*-quinol 4: (a) H_2, 10% Pd–C, 25% aq. $NaNO_2$, EtOH, rt, 4 h, 78%; (b) $RuCl_3$, $NaIO_4$, $CeCl_3{\cdot}7H_2O$, EtOAc–CH_3CN–H_2O, rt, 1.5 h, 99%; (c) Ac_2O, Et_3N, DMAP, CH_2Cl_2, 0 °C, 4 h, 83%; (d) $NaBH_4$, CH_2Cl_2, rt, 3 h, 60%.

Streptomyces sp. P371, exhibiting inhibitory activity against the pentagastrin-stimulated acid secretion.[15] The *cis*-diol fragment at C4a–C5 present in **14** was introduced after *cis*-dihydroxylation of **4** using RuO_4,[16] giving rise to all-*cis* triol **12** in 99% yield. The relative configuration of this derivative was demonstrated after an X-ray diffraction study (see ESI†). The selective acetylation of the secondary OH at C-5 present in **12** afforded compound **13** in 83% yield. Finally, the stereoselective reduction of **13** with $NaBH_4$ gave rise to **14**, the aquayamycin-type tricyclic model of angucyclinone P371A1, in 60% yield. The correct configuration at C-6 was assigned after an X-ray diffraction study (see ESI†).

Next, we turned our attention to the synthesis of the other aquayamycin-type tricyclic model (**A** in Scheme 1), lacking the oxygenated substituent at C-5, whose structure is present in several angucyclinones such as gaudimycin C and urdamicynone F (Scheme 4). For this purpose, we considered epoxy *p*-quinol **3** (Scheme 1) as a convenient intermediate to install the angular



Scheme 4 Synthesis of epoxide **3** and tricyclic models **16** and **19**: (a) 33% aq. H_2O_2, 6 M NaOH, MeOH, rt, 3 h, 98%; (b) Al–Hg, $NaHCO_3$, THF–EtOH–H_2O, 0 °C, 45 min, 58%; (c) $NaBH_4$, $CeCl_3{\cdot}7H_2O$, MeOH, −78 °C to rt, 3 h, 95%; (d) $NaBH_4$, EtOH, rt, 1.5 h, 92%; (e) i. LAH, THF, rt, 2 h; ii. flash chromatography, 69%.



Scheme 5 Syntheses of tricyclic models **20** and **21**: (a) $H_2NNH_2{\cdot}H_2O$, AcOH, MeOH, 0 °C to rt, 2 h, 57%; (b) H_2, 10% Pd–C, MeOH, rt, 24 h, 53% for the two steps.

OH at C-4a. Compound **3** was obtained after stereoselective conjugate epoxidation of *p*-quinol **4** with H_2O_2 and NaOH, in 98% yield (Scheme 4).

With epoxy *p*-quinol **3** in hand, we first carried out the synthesis of the all-*cis* trihydroxylated derivative **16**, the tricyclic model of gaudimycin C (Scheme 4). This angucyclinone had been obtained by chemoenzymatic synthesis, starting from a common angucycline precursor 2,3-dehydro-UWM6, by the sequential action of two flavoenzymes, PgaE and PgaM, isolated from *Streptomyces* sp. PGA64.[17] Firstly, the reductive opening of epoxide **3** with Al–Hg gave rise to *cis* diol **15**, whose correct structure was assigned after an X-ray diffraction study (see ESI†). In order to achieve the stereoselective reduction, by the lower face of the carbonyl group at C-6 of **15**, we used both small and bulky reducing agents and, in all cases, the major diastereoisomer observed was the desired all-*cis* triol **16**. The best results were obtained using $NaBH_4$ in the presence of $CeCl_3{\cdot}7H_2O$, affording *cis* triol **16**, as the unique diastereoisomer, in 95% yield.

Another aquayamycin-type angucyclinone, similar to gaudimycin C, is urdamycinone F (Scheme 4),[9a] showing the OH at C-6 in a relative *trans* disposition. Urdamycin F was isolated by Rohr in 1986 from *Streptomyces fradiae*.[18] The access to the tricyclic model **19** was not possible by direct reduction of the carbonyl group at C-6 of **15**, since the major diastereomer resulted from the lower face attack of the hydride to the carbonyl group. We then decided to invert the order of the required steps. Thus, the reduction of epoxy ketone **3** using $NaBH_4$ led to an inseparable 15 : 85 mixture of diols **17** and **18**, in 92% yield, where the major diastereomer resulted from the hydride attack from the upper face of the carbonyl group. The regioselective opening of these epoxides with $LiAlH_4$ gave rise, after chromatographic separation, to triol **19**, the tricyclic model of urdamycinone F, in 69% yield.

We were also interested in two aquayamycin-type angucyclinones namely capoamycin and sakyomicin D, bearing a double bond or saturated carbons at C5–C6 positions (Scheme 5). Capoamycin, obtained from *Streptomyces capoamus*, inhibited the growth of Gram-positive bacteria, yeasts and fungi and prolonged the survival periods of mice bearing Ehrlich ascites carcinoma.[19] The access to **20**, the tricyclic model of capoamycin, was possible after treatment of epoxide **3** under the Wharton reaction[20] conditions, giving rise to the allylic diol **20**, in 57% yield, after flash chromatography. The last synthetic target, sakyomicin D, was isolated[21a] from an actinomycete of genus *Nocardia*, showing activity against Gram-positive bacteria, and characterized[21b] by the saturated bond at C5–C6 (Scheme 5). The corresponding tricyclic model **21** was obtained after Wharton reaction of **3**, as described above, followed by hydrogenation of **20** in the presence of 10% Pd–C, in 53% yield for the two steps.

In summary, the Oxone-mediated oxidative dearomatization of a tricyclic phenol, easily accessible from commercially available materials, led to the corresponding *p*-quinol, a common precursor of six differently substituted highly challenging angularly-oxygenated tricyclic core models of natural angucyclinones.

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