Natural Product Synthesis

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A Concise Total Synthesis of (*R*)-Puraquinonic Acid**

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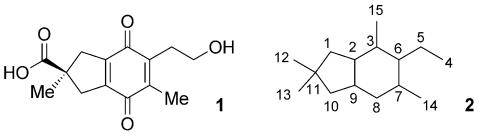
In memory of Robert E. Ireland (1929–2012)

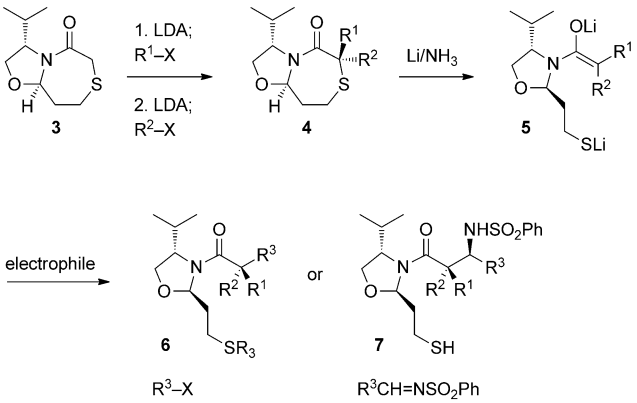
The construction of quaternary carbon stereocenters is among the most difficult challenges in synthesis, one which is compounded when two or more groups at the stereocenter are similar in size and electronics.[1] Puraquinonic acid (**1**, Scheme 1), a 15-norilludalane fungal metabolite, which was



Scheme 1. Structure of (*R*)-puraquinonic acid and the illudalane skeleton.

isolated from mycelial cultures of *Mycena Pura* and which possesses mild differentiation-inducing activity towards HL-60 cells,[2] is an intriguing example of a molecule containing a challenging quaternary stereocenter. The majority of illudalane sesquiterpenoids contain geminal dimethyl groups at C11, which are either prochiral or diastereotopic.[3] In contrast, in the structure of **1**, one of the methyl groups of the geminal dimethyl groups has undergone oxidation resulting in a new quaternary stereocenter. Importantly, the stereodefining groups in **1**, the methyl and hydroxyethyl groups, are far removed from the stereocenter and offer only a minimum of electronic differentiation. Thus, while **1** may appear at first glance to be a simple molecule, its synthesis in enantiopure form is a significant challenge. Indeed, while an efficient 10-step synthesis of racemic **1** has been reported,[4] the only enantioselective synthesis of **1** exceeds 30 steps in length.[5]

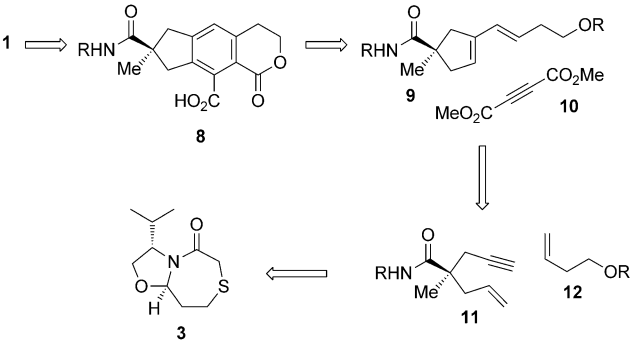
We have previously developed a method for the formation of quaternary stereocenters based on the stereoselective generation and alkylation of α,α-disubstituted amide enolates from easily prepared bicyclic thioglycolate lactam **3** (Scheme 2).[6,7] Sequential double alkylation of bicyclic lactam **3** followed by a dissolving metal reduction results in stereoselective formation of an α,α-disubstituted enolate (**5**), where the enolate geometry is regulated by the combination of the conformation of the starting bicycle and the configuration of the α-stereocenter. The resulting enolate possesses



Scheme 2. A bicyclic lactam auxiliary for selective quaternary stereocenter formation. LDA = lithium diisopropylamide.

a C_2-pseudosymmetric auxiliary and undergoes highly diastereoselective alkylations (**6**) and Mannich additions (**7**).[6c,8] Importantly, the stereoselectivity of enolate generation and subsequent alkylation is based on the order of alkylation and not the size of the substituents, such that quaternary stereocenters bearing three groups of nearly identical size (e.g. ethyl, propyl, and allyl) can be formed with excellent stereoselectivity. We felt that this method would be ideal for the synthesis of **1**, because it would allow for an early-stage introduction of the quaternary stereocenter.

Our retrosynthetic analysis (Scheme 3) suggested that the quinoid ring in **1** might be generated by oxidation of a Diels–Alder adduct of dimethyl acetylenedicarboxylate **10** and diene **9**. Diene **9** could be envisaged as coming from a tandem ring-closing ene–yne/diene–ene cross metathesis of 1,6-enyne **11** and 3-buten-1-ol.[9] Finally, we fully expected that **11** could be generated stereoselectively through a dialkylation/reduction/alkylation sequence using thioglycolate lactam **3**. Impor-



Scheme 3. Retrosynthetic approach to (*R*)-puraquinonic acid.

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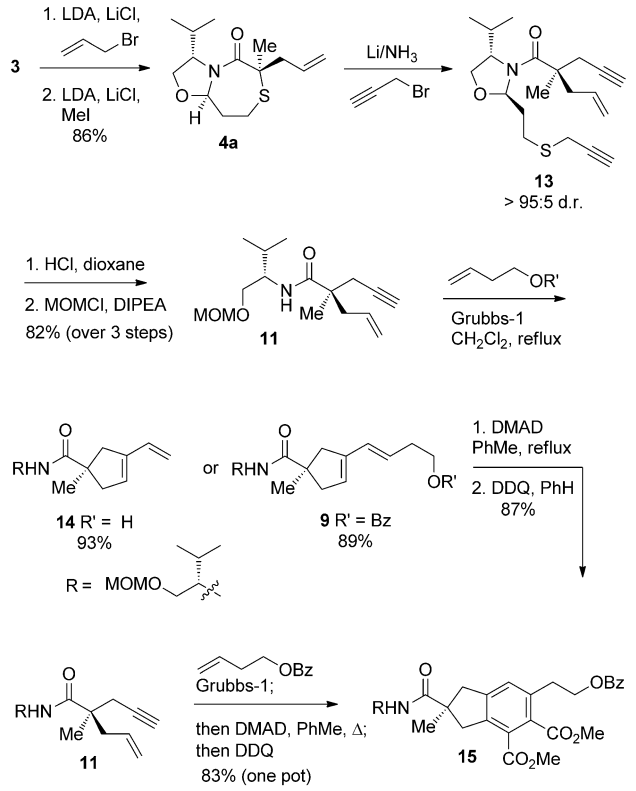
tantly, in this design, a quaternary stereocenter bearing two groups of similar size and similar electronics (allyl and propargyl) would be set at an early stage, and the stereochemistry would be transmuted through the subsequent metathesis and Diels–Alder sequences to eventually produce the distally differentiated quaternary stereocenter.

Diels–Alder precursor **9** was prepared in six steps from bicyclic lactam **3** in 63% overall yield. Sequential alkylation of **3** with allyl bromide followed by methyl iodide provided **4a** in 86% yield as a single stereoisomer (Scheme 4). Reductive

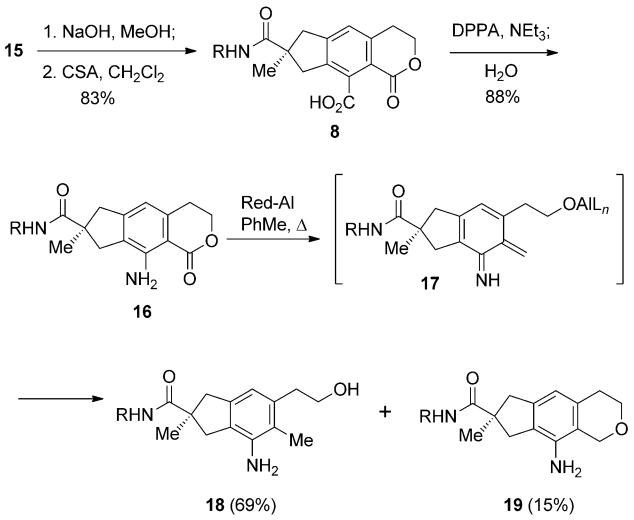


Scheme 4. Formation of the quaternary carbon stereocenter and a metathesis/Diels–Alder sequence. MOMCl = methoxymethyl chloride, DIPEA = *N,N*-diisopropylethylamine, Grubbs-1 = Grubbs catalyst of the first generation, DMAD = dimethyl acetylenedicarboxylate, DDQ = 2,3-dichloro-5,6-dicyano-1,4-benzoquinone.

enolization of **4a** using lithium in ammonia followed by addition of propargyl bromide formed the desired quaternary stereocenter in > 95:5 d.r.[10] The aminal in **13** was hydrolyzed to simplify subsequent NMR spectra (by eliminating amide rotamers) and also to excise the additional propargyl group to avoid possible complications in subsequent metathesis and Diels–Alder chemistry. Treatment with aq. 1M HCl in dioxane at 23°C afforded selective cleavage of the aminal without affecting the amide. Protection of the resulting primary alcohol with methoxymethyl chloride and Hünig's base afforded metathesis precursor **11** in 82% yield over three steps. Attempted ring-closing ene–yne/diene–ene cross metathesis[9] of **11** with 3-buten-1-ol using either Grubbs first- or second-generation catalysts afforded only intramolecular ene–yne metathesis product **14** and the homodimer of 3-buten-1-ol with no cross-metathesis product observed.[11] However, subjection of the benzoate ester of 3-buten-1-ol to the metathesis conditions allowed the formation of cross-metathesis product **9** in 89% yield as a single *E* isomer.

Diels–Alder cycloaddition of diene **9** with dimethyl acetylenedicarboxylate proceeded readily in refluxing toluene without need for Lewis acid catalysts. The resulting diastereomeric mixture of 1,4-cyclohexadienes was directly oxidized with DDQ in benzene to afford arene **15** in 87% yield. Given the need for an ester-protecting group in the metathesis step, we attempted to develop a cascade sequence using the 3-buten-1-yl ester of acetylene dicarboxylic acid, which would undergo the metathesis sequence followed by Diels–Alder cycloaddition. Unfortunately, all attempts at this cascade resulted only in isolation of simple ring-closing product **14**. However, we were able to develop an efficient one-pot process. Conducting the metathesis reaction in dichloromethane followed by a solvent switch to toluene and addition of DMAD followed by treatment with DDQ afforded **15** in 83% yield from **11.**

To differentiate the two methyl esters, **15** was subjected to global saponification to reveal a diacid alcohol, which underwent lactonization using catalytic camphor sulfonic acid in dichloromethane to afford **8** in 83% yield (Scheme 5). To set

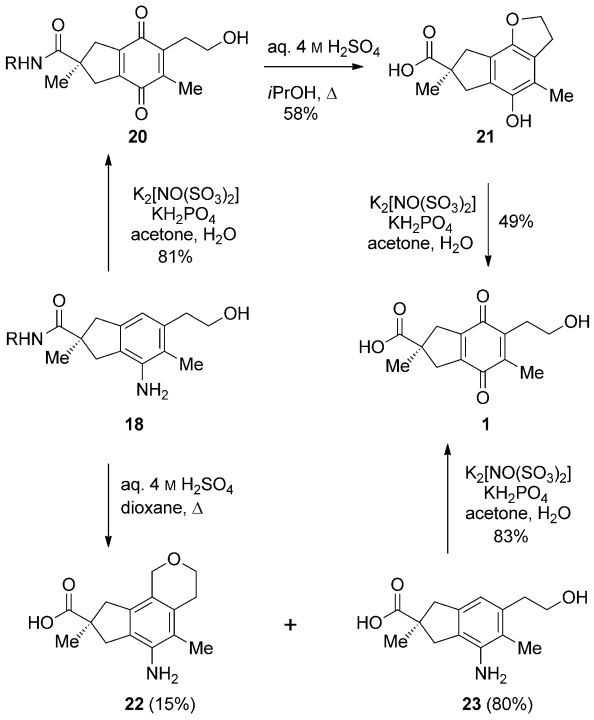


Scheme 5. Core functionalization. CSA = camphor sulfonic acid, DPPA = diphenylphosphorylazide, Red-Al = sodium bis(2-methoxyethoxy)aluminum hydride.

the stage for eventual oxidation to the quinone, the remaining carboxylic acid was transformed into an amine through a Curtius rearrangement. Treatment of **8** with diphenylphosphorylazide followed by aqueous hydrolysis afforded **16** in 88% yield. In a model system, we noted that oxidation of a related aniline to the corresponding quinone could only be achieved when the ring did not bear any electron-withdrawing groups, and thus we sought to reduce the lactone in **16**. We were pleased to find that treatment of **16** with Red-Al in toluene at reflux reduced the lactone to the desired methyl group, thereby affording **18** in 69% yield. Importantly, as long as a large excess of hydride was not employed, the reaction

proceeded without any noticeable reduction of the secondary amide. The reduction was accompanied by the formation of a small amount of dihydropyran **19** (15%). That this was a by-product and not an intermediate on the reduction pathway was supported by the fact that resubmission of **19** to the reduction conditions only resulted in slow reduction of the amide. We presume that the reduction of the lactone to the methyl occurs via an *ortho*-iminoquinone methide intermediate (**17**), which is not easily formed from **19** owing to poor orbital alignment.

To complete the synthesis of **1**, all that was seemingly required was to oxidize to the quinone and remove the chiral auxiliary. Oxidation of **18** could be easily achieved by using Fremy's salt in water/acetone to give the valinol amide of puraquinonic acid (Scheme 6). However, hydrolysis of **20** with



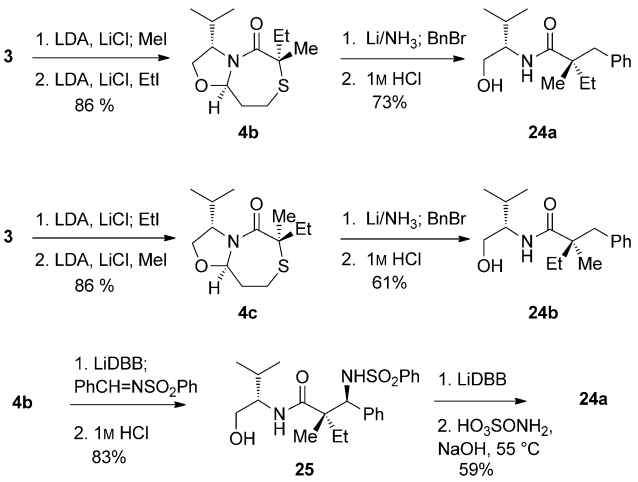
Scheme 6. Completion of the synthesis of puraquinonic acid.

aq. 4 M H_2SO_4 in dioxane at reflux failed to provide the natural product. Although the residual auxiliary was hydrolyzed, the quinone had undergone reductive etherification with the pendant hydroxyethyl group affording **21** in low yield (Scheme 6). Switching the co-solvent from dioxane to isopropanol improved the yield of **21**, but did not solve the reduction problem. Reduction of quinone dimethyl acetals under acidic conditions has been reported, with the most likely reduction source being hydride donation by released methanol,[12] and in the present case, we presume that dioxane and isopropanol can also fill this role. Unfortunately, conducting the hydrolysis without organic co-solvents was inefficient owing to insolubility. Ultimately, hydroquinone ether **21** could be transformed to puraquinonic acid (**1**) by oxidation with Fremy's salt. However, overall this final sequence was inefficient owing to the need to re-oxidize.

An improved route could be achieved by hydrolyzing the auxiliary first. Heating of **18** at reflux in aq. 4 M H_2SO_4/dioxane afforded the desired carboxylic acid **23** in 80% yield. This reaction was accompanied by the formation of dihydropyran **22** in 15% yield, presumably arising from electrophilic aromatic substitution with the formaldehyde released during MOM group cleavage. Finally, the aniline could be cleanly oxidized to the quinone to afford **1** in 83% yield.

Quinone **1** had identical ^1H, ^{13}C NMR, and IR spectroscopic characteristics to those reported.[13] However, the measured specific rotation of $+1.5$ ($c = 0.3$, $CHCl_3$) was opposite to that expected. Based on our methodology, we expected that the synthesis beginning with reduction and alkylation of **3** would ultimately produce (*R*)-**1**, as depicted. In contrast, Clive et al. reported that their synthesis of (*S*)-**1**, wherein the quaternary stereocenter was established via an Evans aldol followed by a radical cyclization, resulted in a positive rotation.[5,14]

Given the discrepancy between our observed rotation and the prior assignment, we reconfirmed the stereochemical outcome of our alkylation sequence. We initially assigned the stereochemistry of the alkylation sequence by comparing the optical rotation of an alkylation product to literature data.[6] As noted above, we have recently extended our enolate chemistry to include Mannich additions to benzenesulfonyl-protected imines.[8] Fortuitously, the stereochemistry of Mannich addition products was assigned unambiguously by X-ray crystallography, and we reasoned that a deamination process would allow direct comparison to products **24a** and **24b** formed from a standard alkylation sequence (Scheme 7). Thus, reduction of Me/Et-substituted lactam **4b** followed by addition to the benzylsulfonylimine of benzaldehyde and subsequent acetal hydrolysis afforded Mannich addition product **25** as reported. The stereochemistry of **25** was reconfirmed by X-ray crystallography and found to be consistent with our prior assignment. Direct hydrogenolytic deamination of **25** proved to be difficult.[15] However a two-step deamination could be achieved by desulfonylation with LiDBB followed by deamination via in situ formation of



Scheme 7. Stereochemical proof for alkylation chemistry. LiDBB = lithium di-*tert*-butylbiphenylide.

a monoalkyl diazene by using hydroxylamine *O*-sulfonic acid.[16] The deamination product proved to be identical to **24a**, which is the major product derived from reduction and alkylation of **4b** with benzyl bromide followed by partial aminal hydrolysis, and was clearly different than **24b**, which is the product derived from an identical sequence on lactam **4c**. This result confirmed that our original assignment of stereochemistry of the alkylation sequence was correct and strongly supports the conclusion that we have prepared (*R*)-puraquinonic acid. We presume that the source of discrepancy between our observed rotation and the literature lies in the small absolute value for rotation, which may render the determination of sign within the error limits of standard polarimetry on small samples.

In conclusion, the stereoselective synthesis of (*R*)-puraquinonic acid has been accomplished in an efficient 12 steps and 20% overall yield. This is the first application of our bicyclic thioglycolate lactam method towards the synthesis of a natural product and highlights the ability to fashion quaternary stereocenters that possess groups with very little steric or electronic difference. In the context of puraqinonic acid, the bicyclic lactam allowed the preparation of a stereocenter bearing allyl and propargyl units, which, through a metathesis and Diels–Alder sequence, could be transmuted to set the deceptively difficult stereochemistry of the natural product.

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