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Enantioselective, intermolecular [2+2] photocycloaddition reactions of 3-acetoxyquinolone: Total synthesis of (−)-pinolinone

Florian Mayr, a Christian Wiegand, a and Thorsten Bach b

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The natural product (−)-pinolinone was synthesised in a concise route (six steps, 17% overall yield) from 3-acetoxyquinolone, employing an enantioselective intermolecular [2+2] photocycloaddition as the key step.

(−)-Pinolinone was described in 2000 as a novel naturally occurring 3,4-dihydroquinolin-2(1H)-one, which was isolated by extracting dried roots of Boronia pinnata Sm. (Rutaceae) with acetone at ambient temperature.1 It belongs to the class of 3-prenylated quinolin-2(1H)-ones, some representatives of which had been previously reported2 but only one as a constituent of the plant genus Boronia.3, 3,4-Dihydroxylation is observed in many naturally occurring 3,4-dihydroquinolin-2(1H)-ones derived from anthranilic acid. However, most of these compounds bear an additional 4-aryl substituent derived from an aromatic amino acid.4

Despite the fact that little information was available on the biological activity of (−)-pinolinone, we became interested in its total synthesis with the goal of proving its constitution and its absolute configuration. Indeed, although the relative configuration of the natural product had been established, there was no information about its absolute configuration and both structures 1 (Scheme 1) and ent-1 were conceivable.

Based on the successful implementation of an enantioselective5 intermolecular [2+2] photocycloaddition approach6 in a previous total synthesis7 of a 3,4-dihydroquinolin-2(1H)-one, (+)-meloscine,2 we considered an addition of an appropriate olefin to 3-acetoxyquinolone (4) as an efficient way to set up the two stereogenic centers of the natural product. Intermediate 3 was to be converted into γ-lactone 2, from which the target compound would be accessible by straightforward transformations. In this communication we disclose the successful execution of this photocycloaddition strategy, which led to the first synthesis of (−)-pinolinone and allowed for the assignment of its absolute configuration.

Previous work by Kobayashi et al. had revealed that 3-acetoxyquinolone (4) is a competent enone substrate in intermolecular [2+2] photocycloaddition reactions.9 Successful reactions with cyclic and acyclic alkenes as well as with an enol ether (2-methoxypropene) were reported. These results are in line with the observation that electron-rich alkenes are good reaction partners in intermolecular quinolone [2+2] photocycloaddition reactions.10 Our plan was to find an appropriate ketene acetal, which would react with sufficient regioselectivity to provide, after hydrolysis a stereo- and regiochemically homogenous cyclobutanone, the Baeyer-Villiger oxidation11 of which would lead to the desired γ-lactone. A second goal of the preliminary work was to probe the suitability of the title compound for enantioselective [2+2] photocycloaddition reactions in the presence of chiral template 612 (Table 1). Among the ketene acetals, which were tested in the racemic reaction (λ = 300 nm, c = 5 mM in acetonitrile) 1,1-diethoxyethene (5e) and silyl enol ether 5f turned out to be best suited. Other olefins that also reacted well and which had not previously studied included vinyl acetate (5a), 1,1-dichloroethene (5b), 2-ethyl-1-butenec (5c) and vinylene carbonate. Yields varied between 62% and 99% (see ESI for additional information). Almost any of the mentioned olefins – apart from vinylidene carbonate – and also the previously studied 2,3-dimethyl-2-butenec (5d) reacted equally well in the templated reaction at −70 °C in toluene. The enantioselectivities were somewhat variable but – given the fact that 3-alkenoyloxy-substituted quinolones had shown relatively low enantioselectivities in template mediated intramolecular [2+2] photocycloaddition reactions13 – it was gratifying to note that in particular the ketene acetics 5e and 5f reacted smoothly with excellent enantioselectivities. Product 3e was obtained in 67% yield and with 95% ee and product 3f was obtained in 97% yield with 88% ee for the major diastereoisomer and with 95% ee for the minor diastereoisomer (d.r. = 71/29).
The regioselectivity of the photocycloaddition was high and products 3a, 3b, 3c, and 3f were potentially suited for conversion into the desired cyclobutanone. The high enantioselectivities achieved for 3e and 3f and the fact that there would be no change of the oxidation state required for 3e and 3f (as opposed to 3a) led us to study the latter two products for conversion into a cyclobutanone. Preliminary experiments were performed with racemic material. The N-methylation of 3,4-dihydroquinolin-2(1H)-one rac-3e was facile employing NaH and MeI in THF (84% yield) but conditions for the smooth hydrolysis of the O,O-acetate could not be found. There was no reaction upon treatment with aqueous HCl or with para-toluenesulfonic acid in THF while an attempted reaction with trifluoroacetic acid led to complete decomposition. Similar observations were made with acetal rac-3f. Neither the compound itself nor its N-methylated derivative could be converted into the desired cyclobutanone (Scheme 2). A major issue with these transformations is the facile retro-aldol cleavage, which can occur in compounds such as rac-7 under basic conditions and which leads to a cyclobutane ring opening. It was suspected that the presence of fluoride ions required for desilylation induces a deacetylation of the tertiary alcohol, which in turn leads to decomposition. Variation of acidic conditions for tert-butyldimethylsilyl (TBS) removal led to the discovery that the protecting group removal can be combined with the desired oxidative Baeyer-Villiger type rearrangement employing meta-chloroperbenzoic acid (mCPBA) as the oxidant in the presence of boron trifluoride as the Lewis acid.15 Although lactone rac-8 was isolated in low yields this discovery opened a viable route for completion of the total synthesis.

Scheme 2 Unsuccessful attempts to convert compound rac-3f into cyclobutanone rac-7 and successful oxidation to lactol rac-8

After N-methylation of enantiomERICALLY enriched compound 3f16 the resulting product 9 underwent the desired oxidative rearrangement in 69% yield. However, it was not possible to perform the required simultaneous reduction of the lactone 4 and the acetate to the desired product 11 in good yields. The sequence was therefore performed stepwise, with the deacetylation preceding the oxidation. Tertiary alcohol 10 was obtained from acetate 9 upon treatment with KCN in ethanol17 and was then oxidized with mCPBA to γ-lactone 2 (Scheme 3). At this stage, the compound (87% ee) was purified by semipreparative chiral HPLC to obtain enantiopure material (≥99% ee).

Scheme 3 Synthetic sequence to (+)-pinolinone (1) from enantiomERICALLY enriched [2+2] photocycloaddition product 3f

In the subsequent reduction of lactone 2 to lactol 11, it was observed that the success of the reaction depends strongly on the solvent and the number of equivalents of disobutylaluminium hydride (DIBAL-H).18 Dichloromethane turned out to be superior to hexane, toluene or ether as the solvent. For complete conversion three equivalents of the reducing agent were required. Lactol 11, which was obtained under optimized conditions in 61% yield, should be in equilibrium with the respective γ-hydroxyaldehyde and it was therefore assumed that a Wittig reaction could be successfully executed. Despite

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*All photochemical reactions were conducted using a RPR-100 reactor with 16 fluorescent lamps (Durian apparatus; for emission spectrum, see ref.15) as the irradiation source in deaerated toluene (c = 5 mM) as the solvent. The irradiation time was three hours. Yields refer to isolated products. Diastereomeric ratio for the two diastereoisomers. For structure assignments, see narrative and ESI. Enantiomeric excess of major and minor diastereoisomer, respectively.

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Table 1 Enantioselective intermolecular [2+2] photocycloaddition reactions of 3-acetoxyquinoline (4) and olefins 5 mediated by chiral template 6

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the extensive literature precedence that exists for this transformation, there is no reaction, in which a γ-lactol was converted to a triply substituted olefin with two methyl groups at the terminal position. A further complication in the projected transformation was the acidity of the tertiary alcohol. Initial attempts to achieve the reaction by addition of the ylide to the lactol remained unsuccessful but it was found that the reaction could be performed at 0 °C by adding the ylide to an excess of the ylide in THF as the solvent. Under these conditions, a yield of 55% could be achieved for the olefination reaction and product 1 was found to be levorotatory, which – based on the known enantioselectivity exerted by template 6–12 – proved the absolute configuration to be (3S,4R). Despite the fact that the enantiopturality of final product 1 was confirmed by chiral HPLC, the specific rotation was lower than the reported value.10

In summary, the first total synthesis of (−)-pinolinone (1) has been accomplished via an enantioselective intermolecular [2+2] photocycloaddition of 3-acetoxyquinolone (4) and an appropriate silyl ketene acetal. Further key steps included a selective ring expansion of the cyclobutane ring to a γ-lactone and the subsequent conversion of the latter compound by a reduction/olefination sequence.

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Notes and references

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2. † Electronic Supplementary Information (ESI) available: See DOI: 10.1039/b000000x/


