

# Enantioselective, intermolecular [2+2] photocycloaddition reactions of 3-acetoxyquinolone: total synthesis of (–)-pinolinone†

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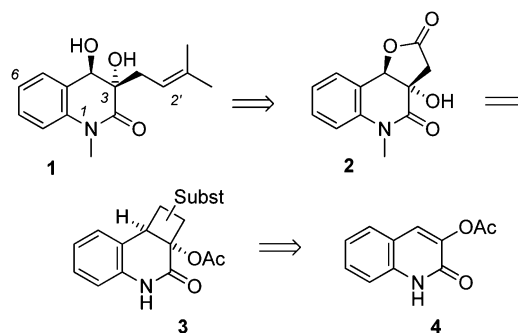
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The natural product (–)-pinolinone was synthesised via a concise route (six steps, 17% overall yield) from 3-acetoxyquinolone, employing an enantioselective intermolecular [2+2] photocycloaddition as the key step.

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

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 enantioselective,<sup>5</sup> intermolecular [2+2] photocycloaddition approach<sup>6</sup> in a previous total synthesis<sup>7</sup> of a 3,4-dihydroquinolin-2(1*H*)-one, (+)-meloscine,<sup>8</sup> we considered the addition of an appropriate olefin to 3-acetoxyquinolone (**4**) to be an efficient way to set up the two stereogenic centers of the natural product. Intermediate **3** was to be converted into  $\gamma$ -lactone **2**, from which the target compound would be accessible by straightforward transformations. In this communication we disclose the successful execution of this photocycloaddition



Scheme 1 Relative configuration of pinolinone (**1**) (ref. 1) and retrosynthetic disconnection leading via intermediates **2** and **3** (Subst = substituents) to the title compound, 3-acetoxyquinolone (**4**).

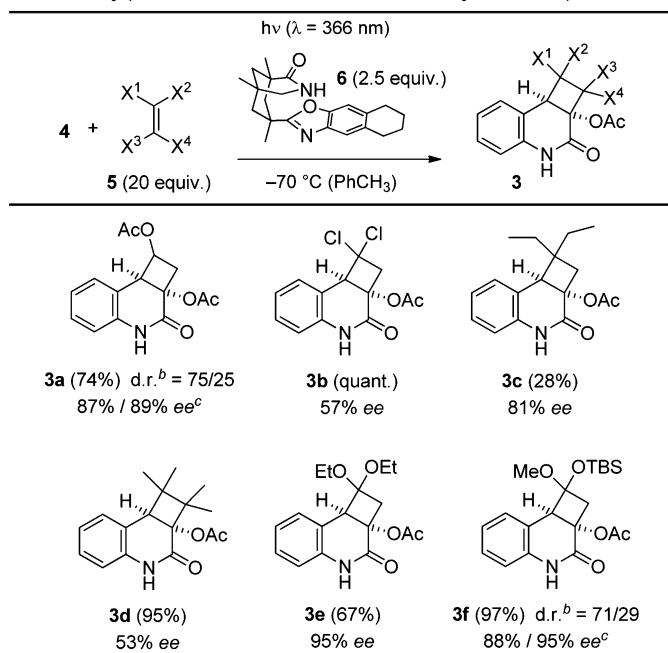
strategy, which led to the first synthesis of (–)-pinolinone and allowed for the assignment of its absolute configuration.

Previous work by Kobayashi *et al.* has revealed that 3-acetoxyquinolone (**4**) is a competent enone substrate in intermolecular [2+2] photocycloaddition reactions.<sup>9</sup> 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.<sup>10</sup> 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 oxidation<sup>11</sup> of which would lead to the desired  $\gamma$ -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 **6** (ref. 12) (Table 1). Among the ketene acetals, which were tested in the racemic reaction ( $\lambda = 366$  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 been previously studied included vinyl acetate (**5a**), 1,1-dichloroethene (**5b**), 2-ethyl-1-butene (**5c**) and vinylene carbonate. Yields varied between 62% and 99% (see the ESI† for additional information). Almost any of the mentioned

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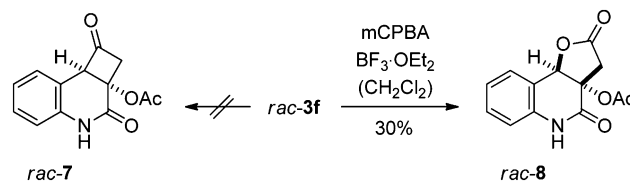


**Table 1** Enantioselective intermolecular [2+2] photocycloaddition reactions of 3-acetoxyquinolone (**4**) and olefins **5** mediated by chiral template **6**<sup>a</sup>

<sup>a</sup> All photochemical reactions were conducted using a RPR-100 reactor with 16 fluorescent lamps (Duran apparatus; for the emission spectrum, see ref. 13) as the irradiation source in deaerated toluene ( $c = 5$  mM) as the solvent. The irradiation time was three hours. Yields refer to isolated products. <sup>b</sup> Diastereomeric ratio for the two diastereoisomers. For structure assignments, see the narrative and ESI. <sup>c</sup> Enantiomeric excess of major and minor diastereoisomers, respectively.

olefins – apart from vinylidene carbonate – and also the previously studied 2,3-dimethyl-2-butene (**5d**) reacted equally well in the templated reaction at  $-70$  °C in toluene. The enantioselectivities were somewhat variable but – given the fact that 3-alkenyloxy-substituted quinolones had shown relatively low enantioselectivities in template mediated intramolecular [2+2] photocycloaddition reactions<sup>13</sup> – it was gratifying to note that in particular the ketene acetals **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**, **3e** 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 materials. The *N*-methylation of 3,4-dihydroquinolin-2(1*H*)-one *rac*-**3e** was facile, employing NaH and MeI in THF (84% yield)<sup>14</sup> but conditions for the smooth hydrolysis of the *O,O*-acetal 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

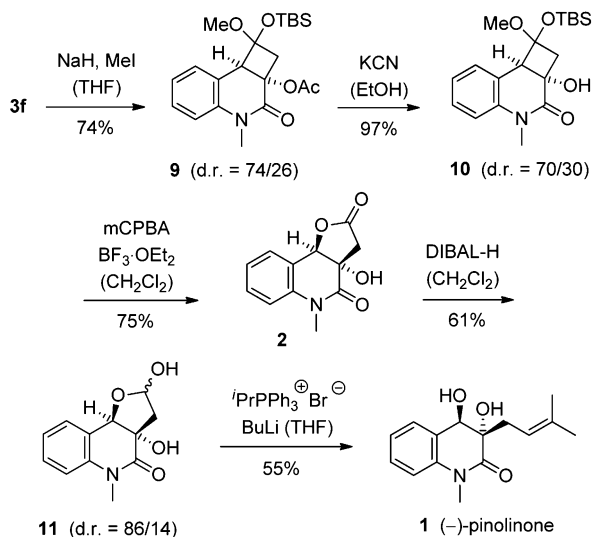
**Scheme 2** Unsuccessful attempts to convert compound *rac*-**3f** into cyclobutanone *rac*-**7** and successful oxidation to lactol *rac*-**8**.

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*-butylsilyldimethylsilyl (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.<sup>15</sup> Although lactone *rac*-**8** was isolated in low yields this discovery opened a viable route for completion of the total synthesis.

After *N*-methylation of enantiomerically enriched compound **3f**<sup>16</sup> 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 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 ethanol<sup>17</sup> and was then oxidized with mCPBA to  $\gamma$ -lactone **2** (Scheme 3). At this stage, the compound (87% ee) was purified by semipreparative chiral HPLC to obtain enantiopure material ( $\geq 99\%$  ee).

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 diisobutylaluminium hydride (DIBAL-H).<sup>18</sup> 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  $\gamma$ -hydroxyaldehyde and it was therefore assumed that a Wittig reaction could be successfully executed. Despite the extensive literature precedence that exists for this transformation,<sup>19</sup> there is no reaction, in which a  $\gamma$ -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 lactol 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 shown to be identical to pinolinone based on its analytical data. The compound was found to be levorotatory, which – based on the known enantioselectivity exerted by template **6** (ref. 6 and 12) – proved the absolute configuration to be (3*S*,4*R*). Despite the fact that the enantiopurity of final product **1** was confirmed by chiral HPLC, the specific rotation was lower than the reported value.<sup>20</sup>





Scheme 3 Synthetic sequence to (–)-pinolinone (**1**) from enantiomerically enriched [2+2] photocycloaddition product **3f**.

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  $\gamma$ -lactone and the subsequent conversion of the latter compound by a reduction/olefination sequence.

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## Notes and references

- C. Ito, M. Itoigawa, T. Otsuka, H. Tokuda, H. Nishino and H. Furukawa, *J. Nat. Prod.*, 2000, **63**, 1344–1348.
- D. Lavie, N. Danieli, R. Weitman and E. Glotter, *Tetrahedron*, 1968, **24**, 3011–3018.
- M. Ahsan, A. I. Gray and P. G. Waterman, *J. Nat. Prod.*, 1994, **57**, 670–672.
- (a) Y. Kimura, M. Kusano, H. Koshino, J. Uzawa, S. Fujioka and K. Tani, *Tetrahedron Lett.*, 1996, **37**, 4961–4964; (b) R. Uchida, R. Imasato, K. Shiomi, H. Tomoda and S. Omura, *Org. Lett.*, 2005, **7**, 5701–5704; (c) K. Scherlach and C. Hertweck, *Org. Biomol. Chem.*, 2006, **4**, 3517–3520; (d) R. Uchida, R. Imasato, H. Tomoda and S. Omura, *J. Antibiot.*, 2006, **59**, 652–658; (e) S. A. Neff, S. U. Lee, Y. Asami, J. S. Ahn, H. Oh, J. Baltrusaitis, J. B. Gloer and D. T. Wicklow, *J. Nat. Prod.*, 2012, **75**, 464–472.
- For recent reviews on enantioselective photochemical reactions, see: (a) C. Yang and Y. Inoue, *Chem. Soc. Rev.*, 2014, **43**, DOI: 10.1039/c3cs60339c; (b) C. Müller and T. Bach, *Aust. J. Chem.*, 2008, **61**, 557–564.
- (a) T. Bach and H. Bergmann, *J. Am. Chem. Soc.*, 2000, **122**, 11525–11526; (b) T. Bach, H. Bergmann, B. Grosch and K. Harms, *J. Am. Chem. Soc.*, 2002, **124**, 7982–7990.
- For reviews on the use of [2+2] photocycloaddition reactions in synthesis, see: (a) J. Iriondo-Alberdi and M. F. Greaney, *Eur. J. Org. Chem.*, 2007, 4801–4815; (b) N. Hoffmann, *Chem. Rev.*, 2008, **108**, 1052–1103; (c) T. Bach and J. P. Hehn, *Angew. Chem., Int. Ed.*, 2011, **50**, 1000–1045.
- (a) P. Selig and T. Bach, *Angew. Chem., Int. Ed.*, 2008, **47**, 5082–5084; (b) P. Selig, E. Herdtweck and T. Bach, *Chem.–Eur. J.*, 2009, **15**, 3509–3525.
- (a) H. Suginome, K. Kobayashi, M. Itoh and S. Seko, *J. Org. Chem.*, 1990, **55**, 4933–4943; (b) K. Kobayashi, M. Suzuki and H. Suginome, *J. Org. Chem.*, 1992, **57**, 599–606.
- (a) B. Loev, M. M. Goodman and K. M. Snader, *Tetrahedron Lett.*, 1968, **9**, 5401–5404; (b) T. S. Cantrell, *J. Org. Chem.*, 1974, **39**, 3063–3070; (c) C. Kaneko, T. Naito and M. Somei, *J. Chem. Soc., Chem. Commun.*, 1979, 804–805; (d) T. Naito and C. Kaneko, *Chem. Pharm. Bull.*, 1980, **28**, 3150–3152; (e) T. Naito, Y. Momose and C. Kaneko, *Chem. Pharm. Bull.*, 1982, **30**, 1531–1534; (f) C. Kaneko, N. Shimomura, Y. Momose and T. Naito, *Chem. Lett.*, 1983, 1239–1242; (g) C. Kaneko, T. Suzuki, M. Sato and T. Naito, *Chem. Pharm. Bull.*, 1987, **35**, 112–123; (h) E. Sato, Y. Ikeda and Y. Kanaoka, *Liebigs Ann. Chem.*, 1989, 781–788; (i) F. Yagishita, T. Mino, T. Fujita and M. Sakamoto, *Org. Lett.*, 2012, **14**, 2638–2641.
- Reviews: (a) C. H. Hassall, *Org. React.*, 1957, **9**, 73–106; (b) G. C. Krow, *Org. React.*, 1993, **43**, 251–798; (c) M. Renz and B. Meunier, *Eur. J. Org. Chem.*, 1999, 737–750; (d) G.-J. ten Brink, I. W. C. E. Arends and R. A. Sheldon, *Chem. Rev.*, 2004, **104**, 4105–4123.
- (a) T. Bach, H. Bergmann and K. Harms, *Angew. Chem., Int. Ed.*, 2000, **39**, 2302–2304; (b) T. Bach, H. Bergmann, B. Grosch, K. Harms and E. Herdtweck, *Synthesis*, 2001, 1395–1405.
- M. M. Maturi, M. Wenninger, R. Alonso, A. Bauer, A. Pöthig, E. Riedle and T. Bach, *Chem.–Eur. J.*, 2013, **19**, 7461–7472.
- (a) M. Uchida, F. Tabusa, M. Komatsu, S. Morita, T. Kanbe and K. Nakagawa, *Chem. Pharm. Bull.*, 1985, **33**, 3775–3786; (b) F. Voss, F. Vogt, E. Herdtweck and T. Bach, *Synthesis*, 2011, 961–971.
- For the use of a Lewis acid ( $\text{SnCl}_4$ ) in an enantioselective Baeyer–Villiger oxidation approach employing a chiral ketal, see: T. Sugimura, Y. Fujiwara and A. Tai, *Tetrahedron Lett.*, 1997, **38**, 6019–6022.
- The starting material for the total synthesis was generated by enantioselective [2+2] photocycloaddition reactions, which were not consistently performed at  $-70\text{ }^\circ\text{C}$  but – due to insufficient cooling – also at slightly elevated temperatures. As known from previous work<sup>6,12</sup> and as detailed in the ESI† the enantioselectivity decreases with increasing irradiation temperature.
- (a) G. J. F. Chittenden, *Carbohydr. Res.*, 1991, **222**, 283–287; (b) C. C. Joseph, H. Regeling, B. Zwanenburg and G. J. F. Chittenden, *Tetrahedron*, 2002, **58**, 6907–6911; (c) L. Kvernø, M. Werder, H. Hauser and E. M. Carreira, *J. Med. Chem.*, 2005, **48**, 6035–6053; (d) S. Hanessian, L. Auzzas, G. Giannini, M. Marzi, W. Cabri, M. Barbarino, L. Vesci and C. Pisano, *Bioorg. Med. Chem. Lett.*, 2007, **17**, 6261–6265.
- (a) M. Babjak, P. Kapitán and T. Gracza, *Tetrahedron*, 2005, **61**, 2471–2479; (b) M. Shoji, T. Uno, H. Kakeya, R. Onose, I. Shiina, H. Osada and Y. Hayashi, *J. Org. Chem.*, 2005, **70**, 9905–9915; (c) N. Joubert, R. Pohl, B. Klepetářová and M. Hocek, *J. Org. Chem.*, 2007, **72**, 6797–6805; (d) D. Enders, A. Hieronymi and G. Raabe, *Synthesis*, 2008, 1545–1558.
- Examples: (a) P. A. Grieco and J. J. Reap, *J. Org. Chem.*, 1973, **38**, 3413–3415; (b) J.-P. Deprés, A. E. Greene and P. Crabbé, *Tetrahedron*, 1981, **37**, 621–628; (c) L. van Hijfte, R. D. Little, J. L. Petersen and K. D. Moeller, *J. Org. Chem.*, 1987, **52**, 4647–4661; (d) G. V. M. Sharma and S. M. Rao, *Tetrahedron Lett.*, 1992, **33**, 2365–2368; (e) Y. Kimura, M. Kusano, H. Koshino, J. Uzawa, S. Fujioka and K. Tani, *Tetrahedron Lett.*, 1996, **37**, 4961–4964; (f) M. Ernst and G. Helmchen, *Angew. Chem., Int. Ed.*, 2002, **41**, 4054–4056; (g) L. S. Hegedus, L. Geisler, A. G. Riches, S. S. Salman and G. Umbricht, *J. Org. Chem.*, 2002, **67**, 7649–7655.
- The reported value for the specific rotation was  $[\alpha]_{\text{D}}^{20} = -9.4$  ( $c = 0.128$ ,  $\text{CHCl}_3$ ).<sup>1</sup> For the synthetic material the specific rotation was determined as  $[\alpha]_{\text{D}}^{20} = -6.3$  ( $c = 0.16$ ,  $\text{CHCl}_3$ ).

