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Catalytic stereoselective total synthesis of a spiro-oxindole alkaloid and the pentacyclic core of tryptoquivalines†

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An expedient route to the pentacyclic core of the tryptoquivaline alkaloids and the total synthesis of natural product (+)-3'-(4-oxoquinazolin-3-yl)spiro[1*H*-indole-3,5'-oxolane]-2,2'-dione (**1**) have been achieved. The route is enabled by a key, highly stereoselective, aldol reaction catalysed by a Ag(I) and cinchona-derived amino-phosphine ligand system, forming a highly substituted oxazoline ring, and setting the C1 spirocyclic stereocentre for downstream manipulation.

Among the large family of quinazolinone alkaloids,^{1–3} tryptoquivalines^{4–6} represent a unique subset characterised by their [5,5]oxo-spirocyclic core, *N,N*-aminal moiety and quinazolinone ring systems (Fig. 1). Previous approaches to construct the spirocyclic core have focussed on oxidative cyclisation approaches. For example, Büchi⁷ (Scheme 1) and Ban⁸ explored oxidative lactonization for establishing the spirocyclic C1 position, with stereocontrol arising from the existing C7 position. Subsequent introduction of the methyl alanine moiety to form the final *N,N*-aminal ring structure then afforded tryptoquivaline L and its C7-epimer. The thermodynamically stable *epi-1* of natural product **1** was chosen by the Büchi group to complete the synthesis of both tryptoquivaline L and C7-*epi*-tryptoquivaline L. In an alternative approach, Nakagawa and co-workers^{9,10} reported an oxidative double cyclization where the generation of the new C1 stereocentre was followed by conversion to tryptoquivaline L, its C7 epimer and *ent*-tryptoquivaline L within a concise synthetic sequence (Scheme 2).

Against these precedents our aim was to develop a new total synthesis of **1** based on a catalytic stereoselective approach to generate the C1 stereocentre which would be independent of any substrate bias, thus potentially enabling access to other family members. Our general strategy to natural product **1**, (+)-3'-(4-oxoquinazolin-3-yl)spiro[1*H*-indole-3,5'-oxolane]-2,2'-dione, is presented in Scheme 3. Pivotal to our approach was the

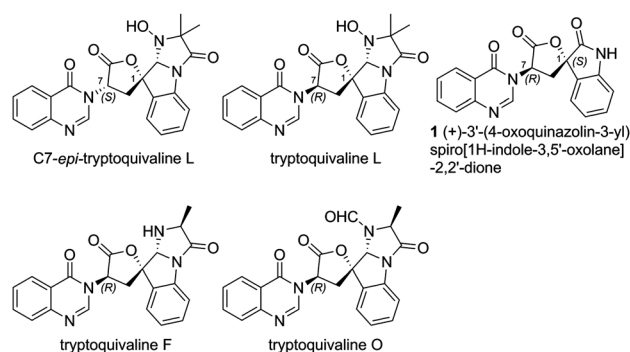
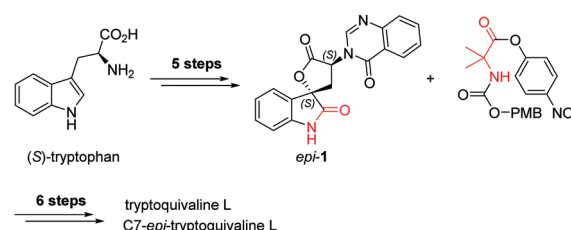


Fig. 1 Selected quinazolinone alkaloids.

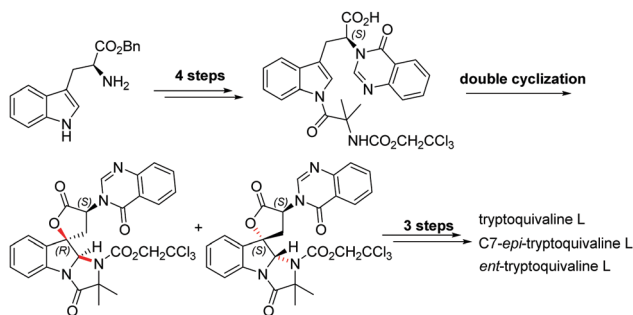
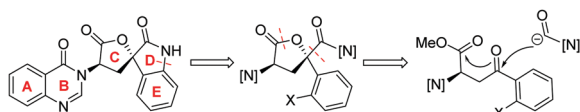
Scheme 1 Previous synthetic route by Büchi *et al.*

stereoselective addition reaction of a masked one-carbon nucleophilic unit into a suitably functionalised quinazolinone-containing aryl ketone derivative where the resulting tertiary alcohol was poised to form the C-ring in a lactonisation process. In turn, the spiro oxindole D-ring could be accessed through a suitable intramolecular C–N coupling reaction. We recognized that the broad-scope silver catalysed enantio- and diastereoselective isocyanoacetate aldol methodology recently developed in our group,^{11,12} Scheme 4, could be applied to deliver the necessary one carbon unit through oxidative manipulation en route to the target.

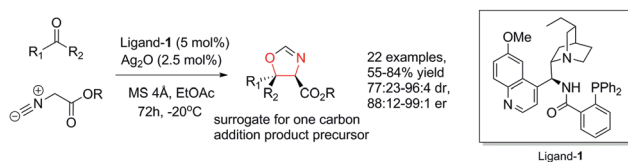
Our route to the key functionalised aryl ketone substrate **5** (poised for the stereoselective isocyanoacetate ketone aldol reaction) is shown in Scheme 5. Starting from commercially

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Scheme 2 Previous synthetic route by Nakagawa *et al.*

Scheme 3 This work synthetic plan.

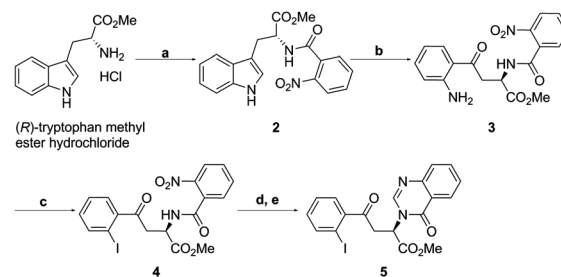
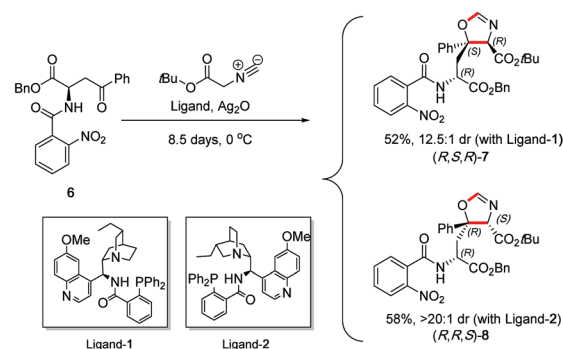


Scheme 4 Underpinning enantioselective isocyanoacetate ketone aldol methodology.

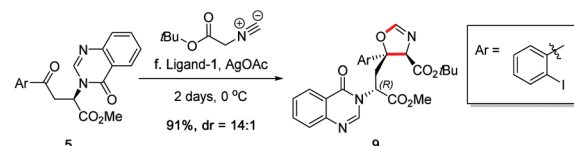
available *D*-tryptophan methyl ester hydrochloride, amine acylation with 2-nitrobenzoyl chloride gave the amide **2** in excellent yield. The indole ring was then subjected to an oxidative cleavage^{13,14} with sodium periodate to afford a mixture of free aniline **3** and its formamide derivative, which upon methanolysis with methanolic HCl, gave aniline **3** in 84% yield. Diazotisation with *tert*-butyl nitrite and subsequent treatment with KI afforded iodoarene **4** in 63% yield. The nitro group of **4** was reduced using iron powder in the presence of ammonium chloride, a method that was sufficiently mild to leave the previously installed iodide intact. Subsequent treatment with trimethyl orthoformate and *p*-toluenesulfonic acid lead to the efficient formation of the quinazolinone ring¹⁵ of desired ketone **5**.

Before carrying out the key stereoselective isocyanoacetate aldol reaction on **5**, the viability of the planned methodology was first investigated on a readily prepared model substrate **6**,§ as shown in Scheme 6. In the study, both quinine and quinidine-derived aminophosphine ligands,¹⁶ ligand-1 and ligand-2 respectively, were tested to ascertain reactivity and stereocontrol. It was found that ligand-1 resulted in a mismatched outcome as shown by a 12.5 : 1 dr, whereas ligand-2 afforded a matched result with a 20 : 1 dr.¶ This study uncovered that the natural diastereoselectivity of the substrate was weak and could be readily overridden with ligand control, thus giving us confidence to perform the reaction on real substrate **5** with accurate prediction of stereochemical outcome.

The key stereoselective reaction was then performed between the chiral aryl ketone **5** and *tert*-butyl isocyanoacetate, catalysed

Scheme 5 (a) 2-Nitrobenzoyl chloride, NaHCO₃, CH₂Cl₂/H₂O, 99%; (b) NaIO₄, MeOH/H₂O; then SOCl₂, MeOH, 84%; (c) HBF₄, *t*BuONO, EtOH, then KI, acetone, 63%; (d) Fe, NH₄Cl, EtOH/H₂O, 95%; (e) pTSA, CH(OMe)₃, CH₃OH, 82%.

Key model reaction

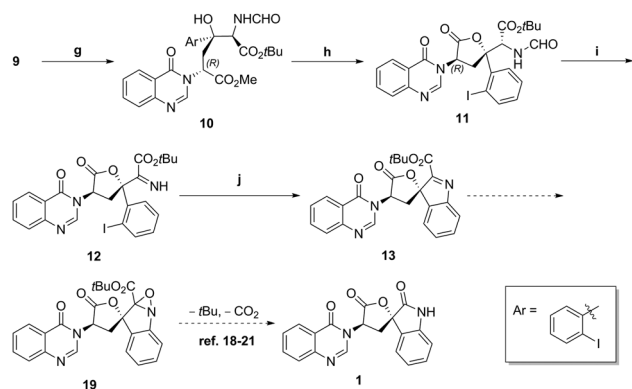


Scheme 6 Key catalyst-controlled isocyanoacetate stereoselective Aldol reaction.

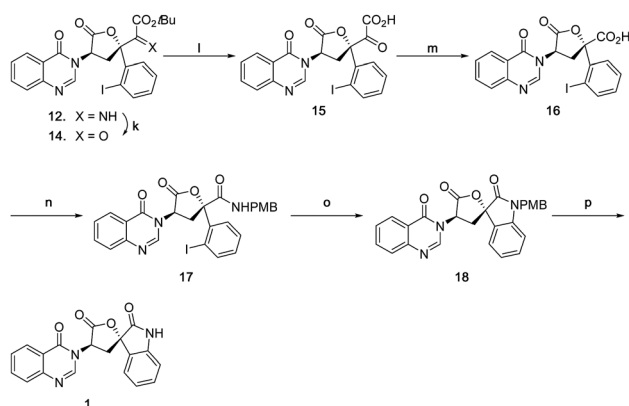
by silver(i) acetate and quinine-derived aminophosphine ligand-1 (Scheme 6) which pleasingly afforded oxazoline **9** bearing two contiguous stereocentres in high yield (91%) and high diastereoselectivity (dr = 14 : 1) on gram scale. The application of this robust and general methodology on the highly functionalized ketone substrate demonstrates its excellent performance, adaptability and functional group tolerance.

The manipulation of isocyanoacetate aldol product **9** into spirocyclic products is shown in Scheme 7. The oxazoline was readily hydrolysed to amino formamide **10** with 1 N hydrogen chloride solution¹¹ in quantitative yield. Then, an acetic acid mediated lactonisation gave lactone **11** in 70% yield. Formamide deprotection with HCl in methanol took place smoothly, and then the amino ester intermediate was oxidized with IBX¹⁷ to give imine **12** in 77% yield. Copper mediated Buchwald type C–N bond formation, to ester indolenine **13** was achieved in 52% yield as shown in Scheme 5. With **13** in hand and inspired by Bode¹⁸ and others,^{19–21} we conceived the decarboxylative rearrangement of oxaziridine intermediate **19** to directly give natural product **1**. However, various conditions failed to realise this transformation.

Accordingly, an alternative sequence to **1** was followed as shown in Scheme 8. Imine **12** was first hydrolysed to α -ketoester



Scheme 7 (g) 1 N HCl, THF, quant; (h) AcOH, toluene, 70%; (i) SOCl₂, MeOH, then IBX, CH₂Cl₂/DMSO, 77%; (j) CuI, Mg(OAc)₂·4H₂O, DMSO, 52%.



Scheme 8 (k) AcOH, THF/H₂O, 73%; (l) TFA/CH₂Cl₂, quant; (m) Ph(OAc)₂, AcOH/H₂O, 80%; (n) PMBNH₂, DIPEA, HATU, CH₂Cl₂/DMF, 70%; (o) CuI, Mg(OAc)₂·4H₂O, DMSO, 70%; (p) TfOH, CH₂Cl₂, 64%.

14 with acetic acid in good yield, then subsequently treated with TFA to afford α -keto acid **15** in quantitative yield. The generated α -keto acid moiety was oxidatively cleaved with PIDA²² to give carboxylic acid **16** in good yield (pyridinium dichromate²³ was far less efficient). Acid **16** was then converted to amide **17** in 70% yield, using a HATU mediated coupling with 4-methoxybenzylamine. The final D-ring was formed by a copper(i) mediated Buchwald type C–N bond coupling condition, giving spiro oxindole **18** in 70% yield. Due to the ease of epimerization at the C7 position, only weak bases were tolerated, magnesium acetate tetrahydrate being found to be optimal. Natural product **1** was finally obtained by deprotection of the PMB group with triflic acid^{24,25} in good yield. The spectroscopic data and specific rotation of the synthetic material were in good agreement with that of the isolated material⁴ confirming the total synthesis of **1** in 15 steps from D-tryptophan methyl ester.

In summary, the catalytic stereoselective total synthesis of natural product **1**, 3'-(4-oxoquinazolin-3-yl)spiro[1H-indole-3,5'-oxolane]-2,2'-dione, was achieved from D-tryptophan methyl ester hydrochloride in a linear route of 15 steps with an overall yield of 6.4%. The key step featured a gram scale catalyst controlled stereoselective aldol reaction to construct the highly

substituted oxazoline ring bearing two contiguous stereo-centres in 91% yield with a dr 14:1, poised for downstream manipulation. Our approach to **1** lays the foundation for further synthetic approaches to quinazolinone alkaloids and the details will be reported in due course.

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Conflicts of interest

There are no conflicts to declare.

Notes and references

‡ Originally reported tryptoquinoline G was structurally revised to tryptoquinoline L (ref. 4) and accordingly in this paper the originally reported tryptoquinoline L was referred to as C7-*epi*-tryptoquinoline L for clarity.

§ For the preparation of **6**, see the ESI.†

¶ Stereochemical configuration was predicted by analogy to previous work and confirmed by NOE on a lactam derivative of (R,S,R)-**7**; see S3 in the ESI.†

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