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Zinc triflate-catalyzed synthesis of pyrazino[2,1-*b*]quinazoline-3,6-diones

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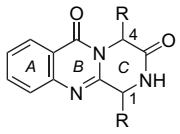
ABSTRACT

Using zinc triflate, the direct one-pot double cyclodehydration of linear tripeptides to the total synthesis of pyrazino[2,1-*b*]quinazoline-3,6-diones (**1a**–**l**) on solid support was achieved with good overall yields in short reaction time. These syntheses of the pyrazino[2,1-*b*]quinazoline-3,6-diones were conveniently achieved in only three steps, starting from the amino acid-bound Wang resin.

1. Introduction

This paper describes, based on a key double cyclodehydration step facilitated by metal triflates, the total synthesis of pyrazino[2,1-*b*]quinazoline-3,6-diones (**1a**–**l**) on solid support. The core structure **1** is common to families of naturally occurring quinazoline alkaloids and a number of them are biologically active.[1] As representative natural products containing the scaffold **1**, luotonin A and its synthetic analogs are known as inhibitors of human DNA topoisomerases[2] and tryptanthrin is anti-inflammatory.[1a,b] In addition, ardeemins, including the naturally occurring *N*-acetylardeemin, are potent agents for reversal of multiple drug resistance in various cancer cell lines.[3] This unique structural feature along with its biological relevance of the aforementioned natural products had stimulated much efforts to develop synthetic approaches to the parent conformationally constrained ring system (**1**).



1,4-dialkyl-2,4-dihydro-1*H*-pyrazino[2,1-*b*]quinazoline-3,6-dione (**1**)

The chemistry and biology of the peptide-derived quinazolinone natural products have recently been reviewed.[1c] In the literature, the access of the core structure **1** was accomplished primarily by three synthetic approaches, starting from quinazolinones, diketopiperazines, or open-chain tripeptides, where anthranilic acid (Abz) can be at the C-terminal, the N-terminal, or the intermediate position of the tripeptide.[1c] As one synthetic approach, several research groups have allotted efforts to the construction of **1** and employed an Eguchi aza-Wittig protocol by selectively acylating diketopiperazines with *o*-azidobenzoyl chloride and subsequently cyclizing to complete the synthesis of a number of fused quinazolinone alkaloids.[1c,4] Alternatively and yet remarkably, Wang and Ganesan[5] adopted the use of triphenylphosphine (Ph_3P) and iodine (I_2) in the presence of Hünig's base (DIEA) (the reagent initially developed by Mazurkiewicz and exploited by Wipf)[6] to achieve a key cyclodehydration of linear tripeptides (D-Trp-Abz-D-Ala and D-Trp-Abz-L-Val), which subsequently led to the total synthesis of two natural alkaloids, fumiquinazoline G and fiscalin B, respectively. Their protocol produced the benzoxazine intermediate followed by deprotection with piperidine and thermal cyclization via a putative piperidine amidine to achieve the final target molecule. Later, Ganesan and co-workers have made use of the same reaction scheme for the synthesis of more complex fumiquinazolines in solution as well as on solid support.[7] Most recently, Liu and co-workers have achieved the syntheses of several pyrazino[2,1-*b*]-quinazoline-3,6-diones (**1**) by means of a one-pot domino procedure that owes its success to microwave heating.[8]

Synthesis of the tripeptide-derived quinazolinone alkaloids essentially exercises in marshalling the amino acid constituents prior to assembling the core **1**. In this report, we aimed at demonstrating that, in conjunction with metal triflates, compounds **1** can be readily prepared on solid support. Our route to natural and

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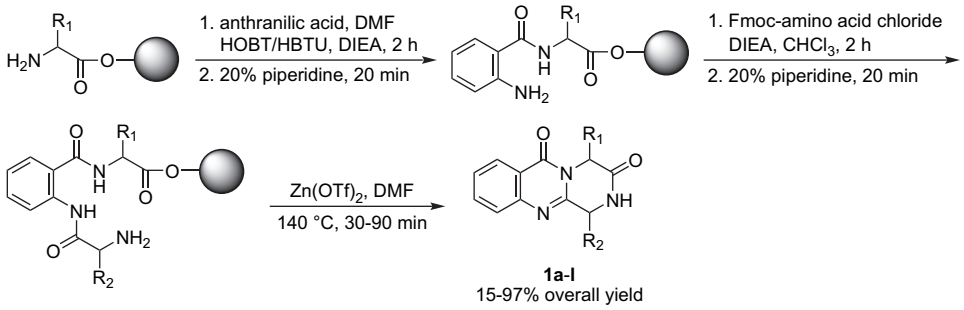


Scheme 1. Solid-phase synthesis of pyrazino[2,1-*b*]quinazoline-3,6-diones (**1a–l**).

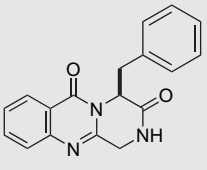
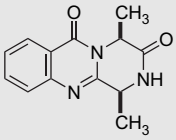
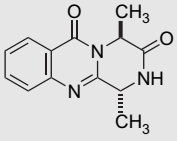
unnatural pyrazino[2,1-*b*]quinazoline-3,6-diones is shown in Scheme 1. Using the standard Fmoc-chemistry of solid-phase peptide synthesis (SPPS), the resin-bound amino acid derivative was sequentially condensed with anthranilic acid and Fmoc-protected amino acid chloride to produce the corresponding tripeptide on solid support (the Wang resin, in this study). Previously, this tripeptide precursor was intramolecularly dehydrated with Ph_3P/I_2/DIEA, subsequently deprotected and cyclized with concomitant detachment from the solid support to finally afford the desired product.[7] This multi-step procedure, however, suffered from the use of a large excess of reagents (5–10 equiv) and very long reaction time, especially when two non-Gly amino acids were involved as parts of the tripeptide substrate;[5,7] the development of alternative protocols therefore is critically needed. In this paper, we wish to report that the aforementioned reaction steps could be conveniently furnished in one single step using Lewis acids such as zinc triflate.

2. Results and discussion

Since metal triflates are useful Lewis acids and have been valuable for facilitating organic reactions,[9] our own examination of the core structure **1** and also a recent reports[10] led us to consider the possibility that **1** might be constructed from its tripeptide precursor by an intramolecular dehydration reaction catalyzed using such Lewis acids. Although this strategy seemed to be rather direct, it was difficult to predict its outcome and, if it worked, the scope of cyclodehydration reactions catalyzed by Lewis acids could potentially be expanded to various dehydrative condensations. At first, we randomly selected six metal triflates and one metal chloride available in our laboratory, and carried out the screening to identify Lewis acids that efficiently facilitate the formation of the ring structures **1** from their open-chain precursors. Using the standard procedure of SPPS, anthranilic acid was coupled with resin-bound amino acid using HOBT/HBTU to give a dipeptide, which was subsequently reacted with Fmoc-amino acid chloride in the presence of DIEA in DMF to afford the protected tripeptide. Finally, the piperidine-deprotected tripeptide was treated with equimolar metal triflate in DMF at 140 °C for 45 min and underwent dehydrative cyclization to finally rearrange to achieve the desired product **1** in one step. Our results are summarized in Table 1. The reactions were qualitatively monitored by TLC and promising ones were then quantitatively analyzed by HPLC and structurally confirmed by NMR and MS.

To our delight, two metal triflates, $Sn(OTf)_2$ and $Zn(OTf)_2$, were found to be effective to achieve the total synthesis of pyrazino[2,1-*b*]quinazoline-3,6-diones (**1a–c**). Of metal triflates tested, the least expensive zinc triflate was established to be the most effective Lewis acid to furnish the double cyclodehydration of three linear tripeptides (Gly-Abz-L-Phe, L-Ala-Abz-L-Ala, and D-Ala-Abz-L-Ala) on Wang resin (Table 1). Reaction of Gly-Abz-L-Phe tripeptide with

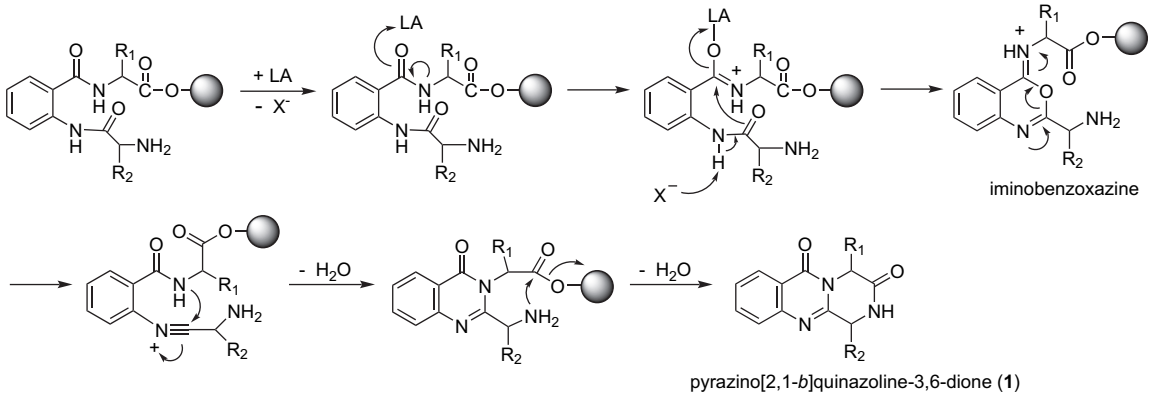
Table 1
Quantitative analysis of Lewis acid catalysts for the double cyclodehydration of three linear tripeptides (Gly-Abz-L-Phe, L-Ala-Abz-L-Ala, and D-Ala-Abz-L-Ala) on Wang resin[a]

Lewis acid	 **1a**		 **1b**		 **1c**	
	Yield[b] (%)		Yield[b] (%)	Cis/trans[c]	Yield[b] (%)	Cis/trans[c]
$Al(OTf)_3$	N.R.[d]		N.R.[d]	—	N.R.[d]	—
$Cu(OTf)_2$	N.R.[d]		N.R.[d]	—	N.R.[d]	—
$La(OTf)_2$	N.R.[d]		N.R.[d]	—	N.R.[d]	—
$Mg(OTf)_2$	N.R.[d]		N.R.[d]	—	N.R.[d]	—
$MgCl_2$	N.R.[d]		N.R.[d]	—	N.R.[d]	—
$Sn(OTf)_2$	14		31	18:82	50	28:72
$Zn(OTf)_2$	56		97	15:85	84	14:86

[a] Reaction condition: resin-bound tripeptide (1 equiv), Lewis acid (1 equiv), DMF, 140 °C, 45 min.
[b] Analytical yield (HPLC).
[c] Cis/trans ratio determined by HPLC.
[d] No reaction.

zinc triflate produced the desired **1a** in 56% overall yield (by HPLC) for three steps, based on the loading of L-Phe-bound Wang resin. We found that this cyclodehydration reaction with concomitant detachment from the resin needed not to be performed in anhydrous DMF solvent, that is, the direct use of on-the-shelf DMF as the reaction medium was sufficed. Interestingly, tin triflate was active, albeit in lower yield (14%); however, $Al(OTf)_3$, $Cu(OTf)_2$, $La(OTf)_2$, $Mg(OTf)_2$, and $MgCl_2$ were totally ineffective (Table 1). It was also worth noting that an increase in molar equivalents of zinc triflate did not improve the yields of reactions (56% for 1 equiv, 46% for 2 equiv, 45% for 5 equiv). The use of sub-stoichiometric amount of $Zn(OTf)_2$ was not attempted in this work. Moreover, upon the second reaction cycle to the same peptide cyclodehydration under the same experimental condition, no more products were formed and detected regardless the Lewis acids used. Evidently, additional reaction time for cyclodehydration and more Lewis acid agent did not increase the yield.

The reaction course of this metal triflate-catalyzed cyclodehydration may be explained on the basis of Scheme 2. Metal triflate is believed to coordinate a carbonyl group on either amides, that is, tripeptide is not intramolecularly dehydrated without metal triflates. The coordination of the carbonyl group on anthranilate to $Zn(OTf)_2$ enhances the electrophilicity of Abz residue, and the subsequent nucleophilic attack of the carbonyl oxygen atom on the N-terminal amino acid affords an intramolecular imidoylation adduct with the benzoxazine structure, followed by a rearrangement catalyzed by the same Lewis acid as well as a concomitant detachment from the second cyclodehydration finally lead to the



Scheme 2. Proposed mechanism for the pyrazino[2,1-*b*]quinazoline-3,6-dione (**1**) formation from the Lewis acid-catalyzed double cyclodehydration of tripeptide in DMF at 140 °C. Though both benzamide and anilide carbonyl groups were accessible to reactions, the benzamide carbonyl group was used here to demonstrate its involvement in reaction mechanism. LA=Lewis acid; X=OTf.

desired quinazoline-3,6-dione product **1** (Scheme 2). From the proposed mechanism, the rearrangement consists in the opening of the ring of the activated imidoylation product by cleavage of the C–O bond, after which the ring closes again in consequence of the formation of the new C–N bond.

Extending the metal triflate-catalyzed cyclodehydration reaction to tripeptides with two chiral centers, L-Ala-Abz-L-Ala and D-Ala-Abz-L-Ala, required additional analysis (**1b** and **1c** in Table 1). Numata and co-workers had previously established that some fumiquinazoline alkaloids were stereoisomers to one another and readily epimerized at both C^1 and C^4 positions under basic conditions (KOH, DIEA, or piperidine), but epimerized only at C^1 with acids (HCl).[11] Due to this possible epimerization at the stereogenic C^1 position under our Lewis acid condition,[7b,11] it could be likely that the cis and trans diastereoisomers of **1b** and **1c** might be detected. As shown in Table 1, we indeed observed that those Lewis acids successful in the tripeptide cyclodehydration epimerized the pyrazino[2,1-*b*]quinazoline-3,6-dione structures (**1b** and **1c**) under our experimental condition. We found that, in the case of $Zn(OTf)_2$, C^1 epimer was produced and both **1b** and **1c** obtained were with similar cis-to-trans ratios, all in favor of the trans isomer (15:85 for **1b** and 14:86 for **1c**). The combined yields of both cis and trans diastereomers for **1b** and **1c** were high (97% and 84%, respectively). Albeit in lower overall combined yields, tin triflate also produced **1b** and **1c** with similar cis-to-trans ratios (18:82 for **1b** and 28:72 for **1c**). Our result suggests that the chemical equilibrium of epimerization occurred under the experimental Lewis acid condition. This result also indicates that the trans product is thermodynamically more stable than its sterically less favorable cis stereoisomer imposed by the pseudoaxial methyl group at C^4 position.[12,13]

We further chromatographically purified individual epimer of **1b** and **1c**, and subsequently investigated possible isomerizations of **1b** to **1c** and **1c** to **1b**. When the pure trans isomer **1c** was treated with $Zn(OTf)_2$ in DMF under the experimental condition (45 min at 140 °C), we detected no conversion of the *trans* **1c** to its *cis* **1b**. Similarly, if the pure *cis* **1b** was treated with $Zn(OTf)_2$ under identical condition, no conversion of **1b** to **1c** was observed and **1b** was fully recovered. This result indicated that, under the Lewis acid condition, the epimerization observed during the synthesis likely took place prior to the second cyclodehydration.

With these encouraging results in hand, we went ahead to prepare more target compounds **1d–l** with greater diversity through this $Zn(OTf)_2$-catalyzed double cyclodehydration process (Table 2). Results of Table 2 show that the target compounds of one chiral center (**1d–f**; compound **1e** is *ent*-glyantrypine) were readily synthesized in 30–45 min and those of two stereogenic centers having sterically bulky groups (**1g–j**), however, required slightly longer reaction times (90 min). The overall isolated yields in this three-step total synthesis were moderate to high. Compounds **1i** and **1j** were successfully obtained by following the $Zn(OTf)_2$-catalyzed heating protocol but only in 15% and 20% yield, respectively, which could be attributed to the steric hindrance created by the disubstituted bulky side chains: the isopropyl group on Val and the benzyl group on Phe.[14] Despite the evidence of epimerization, the successful application of this protocol to access sterically hindered **1i** and **1j** demonstrates the utility of this new method. As shown in Table 2, trans compound was the major product in all cases (**1g–j**). In brief, the results indicate that our solid-phase synthesis is an effective means of preparing constrained peptidomimetics of **1** ring structure. Our synthetic pyrazino[2,1-*b*]quinazoline-3,6-diones showed ^1H and ^{13}C NMR spectra in agreement with the data reported in the literature.[7e]

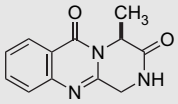
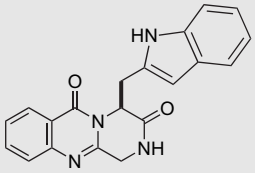
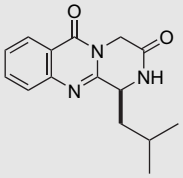
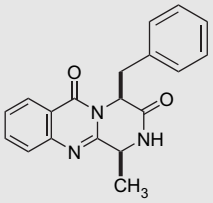
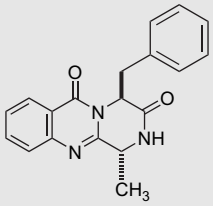
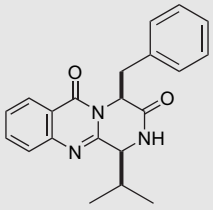
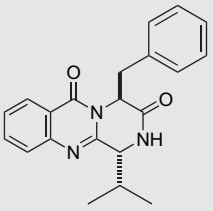
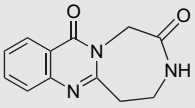
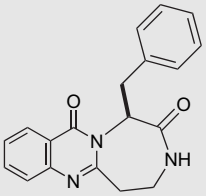
^1H NMR was informative in the structural characterization of pyrazino[2,1-*b*]quinazoline-3,6-diones. Since the C^4 alkyl group always adopts a pseudoaxial disposition and this C^4–H bond is nearly coplanar with the C^6=O group, therefore the quasi-equatorial C^4 proton is characteristically deshielded (5.3–5.7 ppm) in the ^1H NMR spectra for all compounds.[12,13] Moreover, the chemical shift at δ=2.7–3.0 ppm for C^1 hydrogen in *trans* **1h** and **1j** clearly indicates folding of the C^4 benzyl group over the piperazine ring C (4.0–4.5 ppm for their cis epimers). Accordingly, the *cis* **1g** and **1i** show the shielding effect of the phenyl group on the C^1 methyl hydrogens (δ=0.76 ppm) on **1g** and the isopropyl CH hydrogen (δ=1.16 ppm) on **1i**, respectively (1.48 and ca. 2.76 ppm for their corresponding trans epimers).

We have also investigated the formation of ring-expanded target molecules **1k** and **1l** from their linear tripeptide precursors, Gly-Abz-β-Ala and L-Phe-Abz-β-Ala, using $Zn(OTf)_2$ (Table 2). In these cases, β-Ala was used rather than α-amino acid. Following cyclodehydration and cyclative cleavage, low amounts of the desired [1,4]diazepino[7,1-*b*]quinazoline-2,11-diones **1k** and **1l** were isolated: 20% and 7%, respectively.

3. Conclusion

We demonstrated in this study that the double cyclodehydration of linear tripeptides on Wang resin to pyrazino[2,1-*b*]quinazoline-3,6-diones (**1a–l**) could be facilitated by metal triflates. Remarkably, these total syntheses of **1a–l** were achieved in only three steps. This new procedure may lead to the possibility in future evaluation of new Lewis acid optimization for improved synthesis of natural and unnatural quinazoline alkaloids. Further study to extend the scope of its utility is in progress in our laboratory. In the present study, zinc triflate was shown to be the most

Table 2
Representative examples of pyrazino[2,1-*b*]quinazoline-3,6-diones (**1d–l**) prepared from $Zn(OTf)_2$-catalyzed double cyclodehydration of the corresponding tripeptides on Wang resin in DMF at 140 °C[a]

Compound	Reaction time (min)	Isolated yield (%)	Cis/trans
1d 	30	43	—
1e 	45	25	—
1f 	30	67	—
1g 	90	52	25:75
1h 	90	48	24:76
1i 	90	15	31:69
1j 	90	20	23:77
1k 	60	20	—
1l 	90	7	—

[a] Reaction condition: resin-bound tripeptide (1 equiv), Lewis acid (1 equiv), DMF, 140 °C.

effective Lewis acid in facilitating the double cyclodehydration reactions of tripeptides on Wang resin.[15]

4. Experimental

4.1. General experimental section

Flash chromatography was performed on silica gel (230–400 mesh). TLC was carried out on aluminum-backed silica plates pre-coated with silica (0.2 mm), which were developed using standard visualizing agents such as UV fluorescence and iodine. Unless otherwise indicated, all reactions were carried out without the aid of dry nitrogen or argon. NMR spectra were recorded on a Bruker AVANCE DPX 400 at 400 MHz (^{1}H) and 100.6 MHz (^{13}C) both in $CDCl_3$ unless otherwise stated. Chemical shifts were quoted in parts per million (ppm). Melting points were determined on a Fargo MP-2D apparatus (Taiwan, ROC) and are uncorrected. Solvents and reagents were obtained from commercial sources and were used without further purification.

4.2. General procedure for solid-phase synthesis of pyrazino[2,1-*b*]quinazoline-3,6-diones (1a–l)

Fmoc-L-amino acid-Wang resin (Phe, Ala, Trp, Gly) was treated with 20% piperidine in DMF for 20 min and worked up. To the deprotected amino acid-bound resin (1 equiv) were added anthranilic acid (4 equiv), coupling reagent (HOBT and HBTU in DMF, 250 mM, 4 equiv), and DIEA (10 equiv). The reaction was carried out at room temperature for 2 h. The resin was washed with DMF, CH_2Cl_2, and finally isopropyl alcohol.

To the above resin (1 equiv) in $CHCl_3$ were added DIEA (10 equiv) and Fmoc-amino acid chloride (5 equiv). The reaction was performed at ambient temperature for 2 h and worked up. After removing Fmoc protecting group, the tripeptide resin was mixed with zinc triflate (1 equiv) in DMF. The solution was heated at 140 °C for 30–90 min. The mixture was filtered, and the resin was washed with methanol and then with ethyl acetate. The combined filtrates were concentrated to afford the crude product. Purification was accomplished by flash column chromatography (2.5–5% methanol in CH_2Cl_2) to finally achieve the total synthesis of pyrazino[2,1-*b*]quinazoline-3,6-diones.

*4.2.1. (4S)-4-Benzyl-1H-pyrazino[2,1-b]quinazoline-3,6-dione (**1a**)*

White solid; mp 157–158 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.80 (d, J=16.8 Hz, NHC*H*, 1H), 3.49 (d, J=4.0 Hz, CH_2Ph, 2H), 3.93 (dd, J=16.8, 4.4 Hz, NHC*H*, 1H), 5.62 (t, J=4.4 Hz, COCH, 1H), 6.98 (br s, NH, 1H), 6.98 (d, J=6.8 Hz, ArH, 2H), 7.23 (t, J=7.2 Hz, ArH, 2H), 7.30 (m, ArH, 1H), 7.55 (t, J=7.2 Hz, ArH, 1H), 7.60 (d, J=8.0 Hz, ArH, 1H), 7.80 (t, J=7.2 Hz, ArH, 1H), 8.36 (d, J=7.6 Hz, ArH, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 37.1, 44.5, 57.0, 120.1, 126.9, 127.0, 127.2, 128.0, 128.9, 129.8, 134.8, 135.0, 147.1, 148.1, 160.5, 168.7; FAB-HRMS m/z $[M+H]^+$ calcd for $C_{18}H_{16}N_3O_2$ 306.1243, found 306.1238.

*4.2.2. (1S,4S)-1,4-Dimethyl-2,4-dihydro-1H-pyrazino[2,1-b]-quinazoline-3,6-dione (**1b**)*

White solid; mp 169–171 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.76 (d, J=2.6 Hz, CH_3, 3H), 1.77 (d, J=2.6 Hz, CH_3, 3H), 4.76 (q, J=4.0 Hz, NHC*H*, 1H), 5.32 (q, J=7.1 Hz, COCH, 1H), 7.09 (br s, NH, 1H), 7.50 (t, J=7.6 Hz, ArH, 1H), 7.65 (d, J=8.2 Hz, ArH, 1H), 7.78 (t, J=7.4 Hz, ArH, 1H), 8.30 (d, J=8.0 Hz, ArH, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 19.3, 24.9, 51.8, 52.5, 120.2, 126.8, 126.9, 127.1, 134.8, 147.2, 151.0, 160.5, 169.3; FAB-HRMS m/z $[M+H]^+$ calcd for $C_{13}H_{14}N_3O_2$ 244.1086, found 244.1084.

*4.2.3. (1R,4S)-1,4-Dimethyl-2,4-dihydro-1H-pyrazino[2,1-b]-quinazoline-3,6-dione (**1c**)*

White solid; mp 154–159 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.66 (d, J=7.2 Hz, CH_3, 3H), 1.80 (d, J=6.5 Hz, CH_3, 3H), 4.74 (q, J=6.4 Hz,

NHC*H*, 1H), 5.51 (q, *J*=7.1 Hz, COCH, 1H), 6.77 (s, NH, 1H), 7.51 (t, *J*=7.3 Hz, ArH, 1H), 7.70 (d, *J*=8.0 Hz, ArH, 1H), 7.70 (d, *J*=7.2 Hz, ArH, 1H), 8.29 (d, *J*=7.8 Hz, ArH, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 16.5, 17.6, 49.3, 52.4, 120.4, 126.8, 127.3, 127.5, 134.6, 147.0, 150.7, 160.4, 170.0; FAB-HRMS *m*/*z* $[M+H]^+$ calcd for $C_{13}H_{14}N_3O_2$ 244.1086, found 244.1083.

*4.2.4. (4S)-4-Methyl-1H-pyrazino[2,1-b]quinazoline-3,6-dione (**1d**)*

White solid; mp 196–197 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.50 (d, *J*=6.8 Hz, CH_3, 3H), 4.23 (d, *J*=16.7 Hz, NHCH_2, 1H), 4.78 (d, *J*=16.6 Hz, NHCH_2, 1H), 5.01 (q, *J*=7.2 Hz, COCH, 1H), 7.52 (t, *J*=7.5 Hz, ArH, 1H), 7.62 (d, *J*=8.2 Hz, ArH, 1H), 7.82 (t, *J*=7.5 Hz, ArH, 1H), 8.12 (d, *J*=8.0 Hz, ArH, 1H), 8.59 (br s, NH, 1H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 16.3, 44.2, 51.8, 120.1, 126.4, 126.9, 127.1, 134.9, 147.3, 149.5, 159.8, 168.5; FAB-HRMS *m*/*z* $[M+H]^+$ calcd for $C_{12}H_{12}N_3O_2$ 230.0930, found 230.0929.

*4.2.5. (4S)-4-((Indol-2-yl)methyl)-1,2-dihydro-4H-pyrazino[2,1-b]-quinazoline-3,6-dione (**1e**, ent-glyantrypine)*

White solid; mp 156–158 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.82 (d, *J*=16.8 Hz, NHCH_2, 1H), 3.65 (dq, *J*=18.0, 5.2 Hz, indolyl-CH_2, 2H), 3.80 (dd, *J*=16.8, 3.6 Hz, NHCH_2, 1H), 5.63 (q, *J*=2.9 Hz, COCH, 1H), 6.20 (br s, NH, 1H), 6.69 (d, *J*=2.1 Hz, ArH, 1H), 6.93 (t, *J*=7.6 Hz, ArH, 1H), 7.13 (t, *J*=7.7 Hz, ArH, 1H), 7.30 (t, *J*=8.2 Hz, ArH, 1H), 7.40 (d, *J*=8.0 Hz, ArH, 1H), 7.54 (q, *J*=7.8 Hz, ArH, 1H), 7.78 (t, *J*=6.4 Hz, ArH, 1H), 8.37 (br s, NH, 1H), 8.39 (d, *J*=1.5 Hz, NH, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 27.1, 44.6, 56.8, 109.0, 111.2, 118.4, 120.0, 120.1, 122.6, 123.7, 126.7, 126.9, 127.1, 127.2, 134.9, 136.0, 147.1, 148.3, 160.1, 169.5; FAB-HRMS *m*/*z* $[M+H]^+$ calcd for $C_{20}H_{17}N_4O_2$ 345.1352, found 345.1350.

*4.2.6. (4S)-4-(2-Methylpropyl)-2,4-dihydro-1H-pyrazino[2,1-b]-quinazoline-3,6-dione (**1f**)*

White solid; mp 151–153 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.00 (d, *J*=5.8 Hz, CH_3, 3H), 1.05 (d, *J*=5.8 Hz, CH_3, 3H), 1.76–1.86 (m, $(CH_3)_2CH$, 1H), 1.89 (t, *J*=5.7 Hz, $(CH_3)_2CHCH_2$, 2H), 4.42 (d, *J*=18.4 Hz, COCH, 1H), 4.56–4.60 (m, NHC*H*, 1H), 5.03 (d, *J*=18.4 Hz, COCH, 1H), 7.49 (t, *J*=7.7 Hz, ArH, 1H), 7.67 (d, *J*=8.1 Hz, ArH, 1H), 7.77 (t, *J*=7.3 Hz, ArH, 1H), 8.04 (br s, NH, 1H), 8.27 (d, *J*=7.9 Hz, ArH, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.9, 23.0, 25.0, 40.7, 45.1, 54.2, 120.4, 127.0, 127.3, 134.8, 147.1, 148.2, 160.4, 169.8; FAB-HRMS *m*/*z* $[M+H]^+$ calcd for $C_{15}H_{18}N_3O_2$ 272.1399, found 272.1392.

*4.2.7. (1S,4S)-4-Benzyl-1-methyl-2,4-dihydro-1H-pyrazino[2,1-b]-quinazoline-3,6-dione (**1g**)*

White solid; mp 145–148 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.76 (d, *J*=6.8 Hz, CH_3, 3H), 3.47 (d, *J*=11.4 Hz, CH_2Ph, 1H), 3.59 (dd, *J*=5.4, 14.0 Hz, CH_2Ph, 1H), 4.52 (q, *J*=5.0 Hz, NHC*H*, 1H), 5.46 (br s, COCH, 1H), 6.92–6.94 (m, ArH, 2H), 7.19–7.21 (m, ArH, 3H), 7.48 (t, *J*=7.4 Hz, ArH, 1H), 7.62 (d, *J*=8.0 Hz, ArH, 1H), 7.76 (t, *J*=7.4 Hz, ArH, 1H), 7.96 (s, NH, 1H), 8.33 (d, *J*=7.8 Hz, ArH, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 22.9, 36.7, 51.8, 56.7, 119.8, 126.7, 126.8, 126.9, 127.5, 128.8, 130.1, 134.8, 135.2, 147.1, 151.1, 160.7, 167.1; FAB-HRMS *m*/*z* $[M+H]^+$ calcd for $C_{19}H_{18}N_3O_2$ 320.1399, found 320.1398.

*4.2.8. (1R,4S)-4-Benzyl-1-methyl-2,4-dihydro-1H-pyrazino[2,1-b]-quinazoline-3,6-dione (**1h**)*

Light yellow solid; mp 164–168 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.48 (d, *J*=6.1 Hz, CH_3, 3H), 3.03 (q, *J*=6.3 Hz, NHC*H*, 1H), 3.42 (br s, CH_2Ph, 2H), 5.65 (t, *J*=4.6 Hz, COC*H*, 1H), 6.99 (d, *J*=7.2 Hz, ArH, 2H), 7.18–7.29 (m, ArH, NH, 4H), 7.54 (t, *J*=7.3 Hz, ArH, 1H), 7.65 (d, *J*=7.8 Hz, ArH, 1H), 7.78 (d, *J*=7.0 Hz, ArH, 1H), 8.34 (d, *J*=7.4 Hz, ArH, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 18.7, 36.9, 48.9, 57.6, 120.1, 126.8, 127.2, 127.4, 127.8, 128.8, 129.7, 134.7, 135.0, 147.0, 151.5, 160.6, 168.8; FAB-HRMS *m*/*z* $[M+H]^+$ calcd for $C_{19}H_{18}N_3O_2$ 320.1399, found 320.1391.

*4.2.9. (1S,4S)-4-Benzyl-1-isopropyl-2,4-dihydro-1H-pyrazino-[2,1-b]quinazoline-3,6-dione (**1i**)*

White solid; mp 81–82 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.84 (d, *J*=6.5 Hz, CH_3, 3H), 0.96 (d, *J*=6.5 Hz, CH_3, 3H), 1.16 (m, $(CH_3)_2CH$, 1H), 3.49 (d, *J*=5.2 Hz, CH_2Ph, 2H), 4.04 (d, *J*=5.1 Hz, NHC*H*, 1H), 5.48 (t, *J*=5.3 Hz, COCH, 1H), 6.97 (br s, NH, 1H), 7.17–7.23 (m, ArH, 5H), 7.53 (t, *J*=7.4 Hz, ArH, 1H), 7.66 (d, *J*=8.0 Hz, ArH, 1H), 7.80 (t, *J*=7.5 Hz, ArH, 1H), 8.33 (d, *J*=7.8 Hz, ArH, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 18.9, 20.0, 35.0, 38.1, 57.6, 62.0, 120.1, 126.8, 127.2, 127.3, 128.7, 129.9, 134.8, 136.0, 146.8, 149.2, 161.1, 167.4; FAB-HRMS *m*/*z* $[M+H]^+$ calcd for $C_{21}H_{22}N_3O_2$ 348.1712, found 348.1714.

*4.2.10. (1R,4S)-4-Benzyl-1-isopropyl-2,4-dihydro-1H-pyrazino-[2,1-b]quinazoline-3,6-dione (**1j**)*

White solid; mp 189–190 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.73 (d, *J*=6.8 Hz, CH_3, 3H), 0.90 (d, *J*=6.8 Hz, CH_3, 3H), 2.74–2.78 (m, NHC*H*, $(CH_3)_2CH$, 2H), 3.47 (br s, CH_2Ph, 2H), 5.66 (t, *J*=4.0 Hz, COCH, 1H), 6.13 (br s, NH, 1H), 6.93 (d, *J*=7.2 Hz, ArH, 2H), 7.18 (t, *J*=7.6 Hz, ArH, 3H), 7.54 (t, *J*=7.6 Hz, ArH, 1H), 7.62 (d, *J*=8.4 Hz, ArH, 1H), 7.79 (t, *J*=7.2 Hz, ArH, 1H), 8.35 (d, *J*=8.0 Hz, ArH, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.8, 18.9, 29.5, 37.2, 57.0, 57.9, 120.0, 126.9, 127.1, 127.3, 127.8, 128.7, 129.8, 134.8, 134.9, 147.0, 149.9, 160.8, 168.5; FAB-HRMS *m*/*z* $[M+H]^+$ calcd for $C_{21}H_{22}N_3O_2$ 348.1712, found 348.1718.

*4.2.11. 1,2-Dihydro-[1,4]diazepino[7,1-b]quinazolin-4,7(3H,5H)-dione (**1k**)*

White solid; mp 226–228 °C; ^{1}H NMR (400 MHz, CD_3OD) δ 3.46 (dd, *J*=5.6, 7.6 Hz, CH_2, 2H), 3.53–3.61 (m, CH_2, 2H), 5.23 (s, $COCH_2$, 2H), 7.52 (t, *J*=7.8 Hz, ArH, 1H), 7.63 (d, *J*=8.1 Hz, ArH, 1H), 7.80 (dt, *J*=11.2, 7.0 Hz, ArH, 1H), 8.19 (d, *J*=8.0 Hz, ArH, 1H); ^{13}C NMR (100 MHz, CD_3OD) δ 34.3 42.3, 46.6, 121.3, 127.7, 128.0, 128.3, 136.0, 148.4, 158.3, 162.3, 169.4; FAB-HRMS *m*/*z* $[M+H]^+$ calcd for $C_{12}H_{12}N_3O_2$ 230.0930, found 230.0929.

*4.2.12. (5S)-1,2-Dihydro-5-benzyl[1,4]diazepino[7,1-b]quinazolin-4,7(3H,5H)-dione (**1l**)*

Light yellow solid; mp 107–108 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.17–3.21 (m, CH_2, 2H), 3.39 (dd, *J*=13.8, 9.6 Hz, CH_2, 1H), 3.55–3.59 (m, CH_2Ph, CH_2, 3H), 6.17 (br s, NH, 1H), 6.57 (dd, *J*=9.2, 5.2 Hz, COCH, 1H), 7.03–7.04 (m, ArH, 2H), 7.04–7.11 (m, ArH, 3H), 7.40 (t, *J*=7.6 Hz, ArH, 1H), 7.56 (d, *J*=8.0 Hz, ArH, 1H), 7.71 (t, *J*=8.4 Hz, ArH, 1H), 8.05 (d, *J*=8.0 Hz, ArH, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 36.1, 40.4, 41.4, 58.7, 119.9, 126.7, 127.1, 127.3, 127.9, 128.6, 129.4, 134.6, 135.5, 146.4, 155.2, 161.4, 169.9; FAB-HRMS *m*/*z* $[M+H]^+$ calcd for $C_{19}H_{18}N_3O_2$ 320.1399, found 320.1391.

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References and notes

1. For reviews, see: (a) Michael, J. P. *Nat. Prod. Rep.* **2005**, *22*, 627–646; (b) Michael, J. P. *Nat. Prod. Rep.* **2004**, *21*, 650–668; (c) Avendano, C.; Menendez, J. C. *Curr. Org. Chem.* **2003**, *7*, 149–173; (d) Michael, J. P. *Nat. Prod. Rep.* **2003**, *20*, 476–493; (e) Michael, J. P. *Nat. Prod. Rep.* **2002**, *19*, 742–760; (f) Michael, J. P. *Nat. Prod. Rep.* **2001**, *18*, 543–559; (g) Michael, J. P. *Nat. Prod. Rep.* **2000**, *17*, 603–620.
2. (a) Cagir, A.; Jones, S. H.; Eisenhauer, B. M.; Gao, R.; Hecht, S. M. *Bioorg. Med. Chem. Lett.* **2004**, *14*, 2051–2054; (b) Ma, Z.; Hano, Y.; Nomura, T.; Chen, Y.

Bioorg. Med. Chem. Lett. **2004**, *14*, 1193–1196; (c) Cagir, A.; Jones, S. H.; Gao, R.; Eisenhauer, B. M.; Hecht, S. M. *J. Am. Chem. Soc.* **2003**, *125*, 13628–13629.
3. Chou, T.-C.; Depew, K. M.; Zheng, Y.-H.; Safer, M. L.; Chan, D.; Helfrich, B.; Zatorska, D.; Zatorski, A.; Bornmann, W.; Danishefsky, S. J. *Proc. Natl. Acad. Sci. U.S.A.* **1998**, *95*, 8369–8374.
4. (a) Snider, B. B.; Zeng, H. *J. Org. Chem.* **2003**, *68*, 545–563; (b) Hernandez, F.; Lumetzberger, A.; Avendano, C.; Sollhuber, M. *Synlett* **2001**, 1387–1390; (c) Cledera, P.; Avendano, C.; Menendez, J. C. *J. Org. Chem.* **2000**, *65*, 1743–1749.
5. Wang, H.; Ganesan, A. *J. Org. Chem.* **1998**, *63*, 2432–2433.
6. (a) Wipf, P.; Miller, C. P. *J. Org. Chem.* **1993**, *58*, 3604–3606; (b) Mazurkiewicz, R. *Monatsh. Chem.* **1989**, *120*, 973–980.
7. (a) Snider, B. B.; Zeng, H. *Org. Lett.* **2002**, *4*, 1087–1090; (b) Wang, H.; Sim, M. M. *J. Nat. Prod.* **2001**, *64*, 1497–1501; (c) Snider, B. B.; Zeng, H. *Org. Lett.* **2000**, *2*, 4103–4106; (d) Wang, H.; Ganesan, A. *J. Org. Chem.* **2000**, *65*, 1022–1030; (e) Wang, H.; Ganesan, A. *J. Comb. Chem.* **2000**, *2*, 186–194; (f) He, F.; Snider, B. B. *J. Org. Chem.* **1999**, *64*, 1397–1399; (g) Hart, D. J.; Magomedov, N. *Tetrahedron Lett.* **1999**, *40*, 5429–5432.
8. Liu, J.-F.; Ye, P.; Zhang, B.; Bi, G.; Sargent, K.; Yu, L.; Yohannes, D.; Valdino, C. *J. Org. Chem.* **2005**, *70*, 6339–6345.
9. For a recent review, see: Kobayashi, S.; Sugiura, M.; Kitagawa, H.; Lam, W. W.-L. *Chem. Rev.* **2002**, *102*, 2227–2302.
10. For two recent reports on Lewis acid-mediated synthesis of two quinazolino[3,2-*a*][1,4]benzodiazepinediones (asperlicin D and circumdatin F) and a pyrazino[2,1-*b*]quinazoline-3,6-dione (fumiquinazoline F), see: (a) hexamethyldisilazane/I_2: Kshirsagar, U. A.; Mhaske, S. B.; Argade, N. P. *Tetrahedron Lett.* **2007**, *48*, 3243–3246; (b) $MgCl_2$: Al-Said, N. H.; Al-Qaisi, L. S. *Tetrahedron Lett.* **2006**, *47*, 693–694.
11. Epimerization at both C^1 and C^4 positions is possible: (a) Numata, A.; Takahashi, C.; Matsushita, T.; Miyamoto, T.; Kawai, K.; Usami, Y.; Matsumura, E.; Inoue, M.; Ohishi, H.; Shingu, T. *Tetrahedron Lett.* **1992**, *33*, 1621–1624; (b) Takahashi, C.; Matsishita, T.; Doi, M.; Minoura, K.; Shingu, T.; Kumeda, Y.; Numata, A. *J. Chem. Soc., Perkin Trans. 1* **1995**, 2345–2353.
12. Hernandez, F.; Buenadicha, F. L.; Avendano, C.; Sollhuber, M. *Tetrahedron: Asymmetry* **2001**, *12*, 3387–3398.
13. Both X-ray crystallography and ^1H NMR, of the three six-membered rings on the structure **1**, had previously demonstrated that A and B are essentially planar and the pyrazine ring C has a flattened boat conformation. This twisted conformation in **1** leads to the C^4 hydrogen in an equatorial arrangement with an unusual deshielded value in chemical shift and the alkyl group in ring C to adopt a preferred pseudoaxial configuration so that the extremely severe steric interaction between the quinazolone carbonyl group (C^6=O) in ring B and alkyl group at C^4 of ring C can be avoided. See: (a) Suguna, K.; Ramakumar, S.; Rajappa, S. *Acta Crystallogr.* **1982**, *B38*, 1654–1656; (b) Rajappa, S.; Advani, B. G. *J. Chem. Soc., Perkin Trans. 1* **1974**, 2122–2124.
14. Steric hindrance is an important factor in unsuccessful ring formation in fiscalin B total synthesis, see: Buenadicha, F. L.; Avendano, C.; Sollhuber, M. *Tetrahedron: Asymmetry* **2001**, *12*, 3019–3028.
15. Most recently, zinc triflate was found to be an excellent Lewis acid to facilitate the syntheses of heterocycles such as indoles and 4,5-dihydro-3(2*H*)-pyridazinones, starting from terminal alkynes: (a) Alex, K.; Tillack, A.; Schwarz, N.; Beller, M. *Angew. Chem., Int. Ed.* **2008**, *47*, 2304–2307; (b) Alex, K.; Tillack, A.; Schwarz, N.; Beller, M. *Tetrahedron Lett.* **2008**, *49*, 4607–4609.