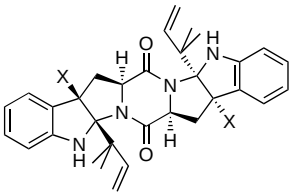
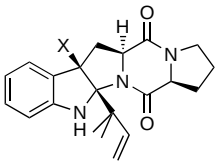
Synthesis of Fluorogypsetin and Fluorobrevianamide E by a Novel Fluorination – Cyclization of *cyclo*-L-Trp-L-AAs**

Norio Shibata,* Takanao Tarui, Yasuhiro Doi, and Kenneth L. Kirk

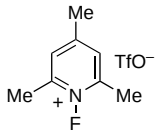
The design of metabolically stable analogues of natural products that have comparable or enhanced biological activity relative to the parent compounds is an important area of research in medicinal chemistry. The incorporation of fluorine atoms into a molecule to inhibit metabolism and/or to alter physicochemical and physiological properties continues to be an important strategy in this research.[1] The replacement of a hydroxyl group by fluorine represents an important and general part of this strategy,[1] and it results in analogues that are often regarded as isosteres of the parent molecules.[2] Thus, the electronegativity and van der Waals radius of fluorine are 4.0 and 1.47 Å, respectively, values that are similar to those of oxygen (3.5 and 1.52 Å).[1, 3a] The C_{sp^3}–F bond of 1.40 Å is slightly shorter than the C_{sp^3}–OH bond (1.43 Å).[3b] Although there are many examples of the effective use of selective fluorination to produce valuable biochemical tools and medicinal agents,[1, 4] examples of fluorine-containing molecules in which a fluorine atom is bound to an asymmetric center are rather limited.[5] In fact, despite the considerable recent progress[6, 7] that has been made in the development of procedures for the enantioselective introduction of fluorine into simple carbonyl compounds, there is concern that application of these procedures to more complex molecules may have serious limitations. Catalytic asymmetric fluorination procedures developed by Hintermann and Togni based on catalysis by chiral Lewis acids,[6d] and by us based on cinchona alkaloids,[7] are new tools to approach this problem. As a part of our research into the development of new methods for the preparation of fluorine-containing biologically active compounds,[7, 8] we have developed a fluorination – cyclization reaction that provides a simple method for the selective introduction of fluorine into complex molecules. To illustrate the utility of this procedure, we report here on the synthesis of fluorogypsetin (**1b**) and fluorobrevianamide E (**2b**) by FP-T300-mediated fluorination – cyclization.



gypsetin (**1a**); X=OH
fluorogypsetin (**1b**); X=F



brevianamide E (**2a**); X=OH
fluorobrevianamide E (**2b**); X=F



FP-T300

The hexahydropyrazino[1′,2′-1,5]pyrrolo[2,3-*b*]indole-1,4-dione moiety is present in a wide range of natural products. Examples are gypsetin (**1a**),[9] brevianamide E (**2a**),[10] and sporidesmins,[11a,b] compounds that have attracted considerable attention due to their molecular complexity and potent biological activity. A similar structural unit also occurs in himastatin,[11c] fumiquinazoline A,[11d] and asperlicin.[11e,f] Gypsetin (**1a**), a promising competitive inhibitor of acyl-CoA:cholesterol acyltransferase, has evoked particular interest as an important lead in drug discovery. After Danishefsky et al. disclosed the first total synthesis of **1a**,[9c,d] we focused on **1b**, an isostere of **1a**, as an attractive synthetic target. We also became interested in the synthesis of the structurally related **2b**. Since the hydroxyl group of **2a**[10] plays an important role in the biosynthesis of brevianamides,[12] **2b** could serve as a useful probe to gain information about biosynthetic processes of the brevianamide family, in addition to having potentially interesting biological activity. Earlier, we reported the selectfluor-mediated oxidative fluorination of indoles to furnish 3-fluorooxindoles.[8a] Since electrophilic attack of fluorine at the 3-position of the indole ring appears to facilitate nucleophilic addition at the 2-position, we reasoned that a suitably positioned internal nucleophile could attack the 3-position to give a cyclized product. To explore this possibility, we initially investigated the reaction of selectfluor with *cyclo*-L-Trp-L-AAs (**3a**–**d**; Trp = tryptophan, AA = amino acid) as a method to produce fluorohexahydropyrazino[1′,2′-1,5]pyrrolo[2,3-*b*]indole-1,4-diones **4** by fluorination – cyclization (Scheme 1, Table 1).

Investigation of the reaction conditions for the selectfluor-mediated cyclization of *cyclo*-L-Trp-L-Ala (**3a**; Ala = alanine) revealed that the choice of solvent is critical. Performing the reaction in MeCN gave a complex mixture (entry 1). The reason for this poor result seemed to be the low solubility of substrate **3a** in MeCN. Therefore, the addition of co-solvents was investigated. The reaction of **3a** in MeCN/DMSO (1/1) gave a 44% yield of fluorinated compound **4a**; addition of THF instead of DMSO gave a similar result (entries 2 and 3). Fluoropyrazinopyrroloindole **4a** was obtained as a 1/1 mix-

[*] Dr. N. Shibata, T. Tarui, Y. Doi
Faculty of Pharmaceutical Sciences
Toyama Medical and Pharmaceutical University
Sugitani 2630, Toyama 930-0194 (Japan)
Fax: (+81) 76-434-4656
E-mail: nozshiba@ms.toyama-mpu.ac.jp
Dr. K. L. Kirk
Laboratory of Bioorganic Chemistry
National Institute of Diabetes and Digestive and Kidney Diseases
National Institutes of Health, Bethesda, MD 20892 (USA)

[**] This work was supported by a Grant-in-Aid for Scientific Research from the Ministry of Education, Science, Sports and Culture, Japan. N.S. wishes to thank the Novartis Foundation (Japan) for the Promotion of Science for support. We thank Prof. Yoshio Takeuchi very much for generously sharing his facilities, for very kind encouragement and for giving us the opportunity to study in the field of fluorine chemistry. We also thank F-TECH INC. for a gift of FP-T300.

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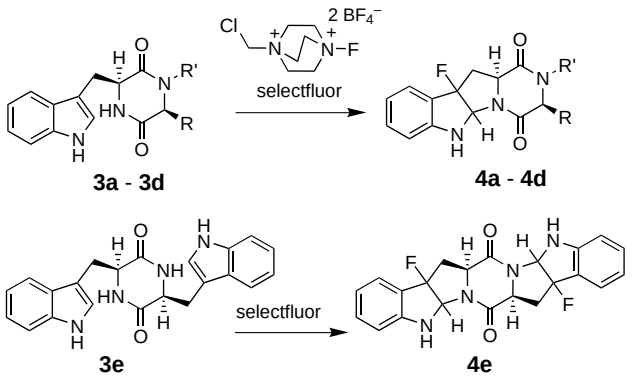


a: R=Me, R'=H; **b**: R=*i*Pr, R'=H; **c**: R=Bn, R'=H;
d: R=R'=$CH_2CH_2CH_2$

Scheme 1. Conversion of *cyclo*-L-Trp-L-AAs **3** into fluorohexahydropyrazino[1′,2′-1,5]pyrrolo[2,3-*b*]indole-1,4-diones **4**. For details see Table 1.

Table 1. Fluorination–cyclization of compounds **3** with selectfluor (Scheme 1).[a]

Entry	Substrate **3**	Solvent	Product **4**	Yield [%]
1	**3a**	MeCN	**4a**	–
2	**3a**	MeCN/DMSO (1/1)	**4a**	44
3	**3a**	MeCN/THF (1/1)	**4a**	48
4	**3b**	MeCN/DMSO (1/1)	**4b**	29
5	**3b**	MeCN/THF (1/1)	**4b**	40
6	**3c**	MeCN/DMSO (1/1)	**4c**	34
7	**3c**	MeCN/THF (1/1)	**4c**	42
8	**3d**	MeCN/THF (1/1)	**4d**	27
9	**3e**	MeCN/THF (1/1)	**4e**	44

[a] The reactions were performed at −40 °C for several hours. The products **4** are mixtures of *syn* and *anti* isomers (1/1), with the exception of **4e**, which is a mixture of three isomers (*syn*,*anti*/*syn*,*syn*/*anti*,*anti* = 2/1/1).[13]

ture of diastereomers in which the fluorine atom is *syn* and *anti* with respect to the proton corresponding to the α-position of L-Trp.[13] To demonstrate the generality of the fluorination–cyclization, we extended the procedure to other *cyclo*-L-Trp-L-AAs **3b**–**e**, including *cyclo*-L-Trp-L-Pro (**3d**; Pro = proline) and *cyclo*-L-Trp-L-Trp (**3e**) (Table 1). In all cases, conversion to **4** proceeded in modest yield. Interestingly, **3e** was converted to the corresponding heptacyclic product **4e** with an efficiency comparable to those of the other reactions, despite the requirement for a crucial double fluorination–cyclization (entry 9). Although an attempted halogenation–cyclization of a *cyclo*-Trp-Ala derivative mediated by *tert*-butyl hypochlorite has been reported,[14] as far as we know, this is the first example of fluorination–cyclization of tryptophan derivatives.

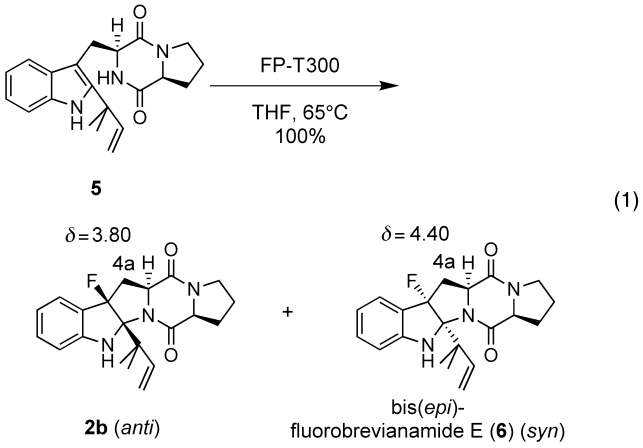
At this point we were gratified that we had succeeded in the first construction of fluoropyrazinopyrroloindoles **4** using a new selectfluor-mediated fluorination–cyclization reaction. However, the yields did not meet our requirements for our planned syntheses of the more challenging molecules **1b** and **2b**. The bulky "reverse-prenyl" substituents present in **1b** and **2b** could present additional problems during the cyclization and thus result in a further decrease in yield. Accordingly, before proceeding with the more challenging syntheses, we conducted a survey of additional electrophilic fluorinating agents. We found that the fluoropyridinium salt FP-T300 was very effective in this process, and produced **4** in good to high yields (Table 2). In the best case, **4b** was formed in 88% yield.

Table 2. Fluorination–cyclization with FP-T300.[a]

Entry	Substrate **3**	Product **4**	Yield [%]
1	**3a**	**4a**	67
2	**3b**	**4b**	88
3	**3c**	**4c**	74
4	**3d**	**4d**	71
5	**3e**	**4e**	74

[a] All reactions were carried out in MeCN at 65 °C for several hours. The products **4** are mixtures of *syn* and *anti* isomers (1/1) except for **4e** (*syn*,*anti*/*syn*,*syn*/*anti*,*anti* = 2/1/1).[13]

Having established the validity of our approach, we now focused on the syntheses of **1b** and **2b**. Under the optimized conditions given above, treatment of reverse-prenylated *cyclo*-L-Trp-L-Pro (**5**), available by total synthesis,[9d] with 1.5 equiv of FP-T300 in THF at 65 °C [Eq. (1)] led to complete



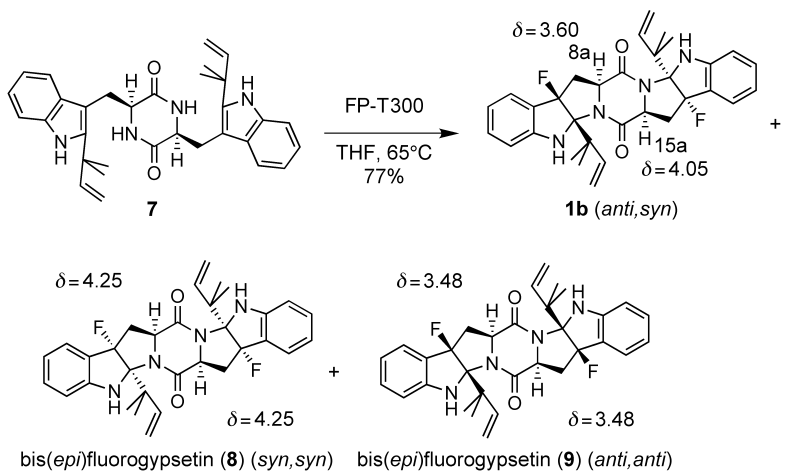
(1)

conversion to give **2b** as a 1:1.6 mixture with the fluorinated bis(*epi*)brevianamide E (**6**). The configuration of each compound was easily determined from the ^{1}H NMR chemical shift of H-4a. Because of the high electronegativity of the *syn*-fluoro substituent, the signal for H-4a of **6** appears at a lower field than that of H-4a of the *anti* isomer **2b** [see Eq. (1)]. This phenomenon is well documented in stereochemical studies on **2a** and its bis-*epi* isomer. In this case the *syn*-proton is similarly deshielded by the *syn*-hydroxyl group.[10c]

On treatment with 3.0 equiv of FP-T300, reverse-prenylated *cyclo*-L-Trp-L-Trp (**7**)[9d] also underwent efficient fluorination–cyclization to give fluorogypsetin (**1b**) and the two bis(*epi*)fluorogypsetins, *syn*,*syn* isomer **8** and *anti*,*anti* isomer **9** (**1b**:**8**:**9** = 2:1:1). Since the *anti*,*syn* isomer is identical to the *syn*,*anti* isomer, the apparent predominant formation of **1b** actually reflects nonselective electrophilic attack of the fluorinating agent from either side of the indole ring with concomitant *trans* addition of nitrogen. Similar to the effects seen with the fluorinated bis(*epi*)brevianamides E, deshielding due to the *syn*-fluorine atom induces a downfield shift of H-15a relative to H-8a. Thus, the ^{1}H NMR chemical shifts of H-8a and H-15a of **1b** were observed at $\delta = 3.60$ and 4.05, respectively [Eq. (2)].

In conclusion, we have developed a general method for the construction of novel fluorohexahydropyrazino[1′,2′-1,5]pyr-

  1433-7851/01/4023-4462 $ 17.50+.50/0 *Angew. Chem. Int. Ed.* **2001**, *40*, No. 23



(2)

rolo[2,3-*b*]indole-1,4-diones based on an electrophilic fluorination–cyclization sequence. We have demonstrated the utility of this procedure by the efficient syntheses of **1b** and **2b**. The biological activities of these alkaloid isosteres will be evaluated and reported subsequently. In addition, we plan to extend application of this new methodology to the synthesis of fluorinated analogues of other indole alkaloids, including himastatin and asperlicin.

Received: June 28, 2001 [Z17385]

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The First Alkaline Earth Metal Complex Containing a μ-η^1:η^1 Allyl Ligand: Structure of $[\{HC[C(tBu)NC_6H_3(CHMe_2)_2]_2Mg(C_3H_5)\}_6]$**

Philip J. Bailey,* Stephen T. Liddle,*
Carole A. Morrison, and Simon Parsons

Recent times have witnessed a surge of interest in the use of β-diketiminates[1] as ancillary ligands in transition metal[2] and main group[3] coordination chemistry. The flexible steric and electronic properties of β-diketiminate ligands, such as **1** (see Scheme 1), make them ideal candidates for the synthesis of well-defined magnesium monoalkyl [(L-X)-Mg-R] complexes; an area that has been recently highlighted as relatively undeveloped,[4] and one which we,[3d, 3g] and others,[3i] have been addressing. Given that there is precedent for the oligomerization and polymerization of ethene by diakylmag-

[*] Dr. P. J. Bailey, Dr. S. T. Liddle, Dr. C. A. Morrison, Dr. S. Parsons
Department of Chemistry
University of Edinburgh
West Mains Road, Edinburgh, EH9 3JJ (UK)
Fax: (+44) 131-6504743
E-mail: Philip.Bailey@ed.ac.uk

[**] The financial support of the UK EPSRC (S.T.L., S.P.) and The Royal Society (C.A.M.) is gratefully acknowledged.

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