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A Convergent Approach to Cyclopeptide Alkaloids: Total Synthesis of Sanjoinine G1

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Abstract: A general strategy for the synthesis of cyclopeptide alkaloids containing an endocyclic aryl−alkyl ether bond has been developed featuring a key intramolecular S_NAr reaction. The importance of the N-terminal protective group in the realization of such a strategy is documented. From the appropriate amino acid constituents, the natural sanjoinine G1, a 14-membered para cyclophane, has been synthesized in seven steps with 21% overall yield.

Introduction

Cyclopeptide alkaloids are para or meta cyclophanes with a polypeptidic tether. The widespread occurrence of these 13-, 14-, and 15-membered macrocyclic molecules in different plants such as rhamnaceae, pendaceae, and rubiaceae has made them an important class of natural products.[1,2] Since the structure elucidation of pandamine (**1**, Figure 1) by Goutarel and Païs in 1964,[3] this family of natural product has grown rapidly and encompasses nowadays a group of over 200 compounds. Although they displayed various interesting biological activities, their limited availability from natural sources has hampered extensive pharmacological investigations.[4] However, Han's group[5] has convincingly demonstrated that sanjoinine-A (frangufoline) (**2**) is the major bioactive component of "Sanjoin", a plant seed of clinical importance in oriental medicine.

Total synthesis of cyclopeptide alkaloids has been investigated by a number of groups, notably those of Païs,[6] Rapoport,[7] Schmidt,[8] Joullié,[9] Lipshutz,[10] and Han.[11] The moderately complex chemical structure of these natural products is in fact a challenging synthetic target. Various strategies based upon macrolactamization, intramolecular Michael addition, intramolecular aldol condensation, and intramolecular amide alkylation have been examined. A seminal contribution results from

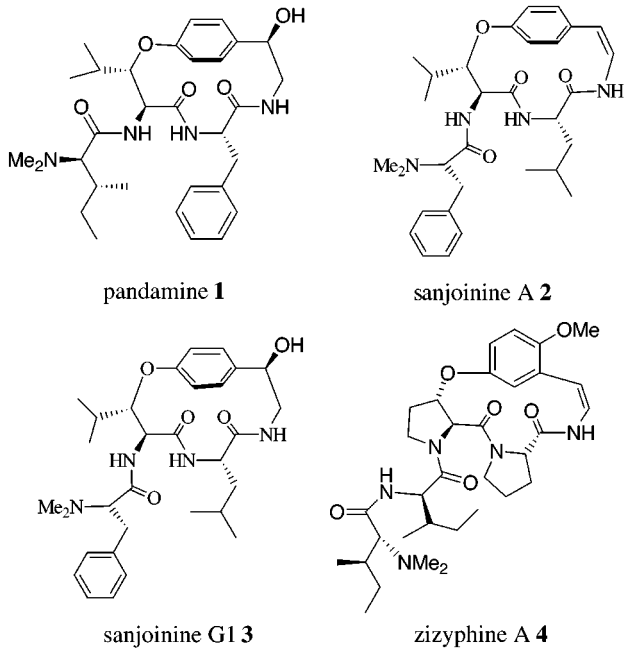

Figure 1.

Schmidt's group who discovered that activation of a carboxyl group as a pentafluorophenyl ester is particularly efficient for the desired macrolactamization. On the basis of this methodology, the same group has accomplished the first total synthesis of zizyphine-A (**4**),[8a] mucronin-B[8e] in 1981, and finally frangulanine,[8h] a 14-membered para cyclophane in 1991. Subsequently, other natural products have been synthesized in Joullié's[9] and Han's groups.[11] Alternatively, an intramolecular N-alkylation using amino oxazole as a masked dipeptide has been elegantly developed by Lipshutz[10] for the construction of natural product analogues. However, intramolecular Michael addition (and its variants), a possible biomimetic approach, failed to produce any cyclic compound probably due to the instability of starting materials and the inherent ring strain associated with the target molecules.[12] It has been thus concluded that cycliza-

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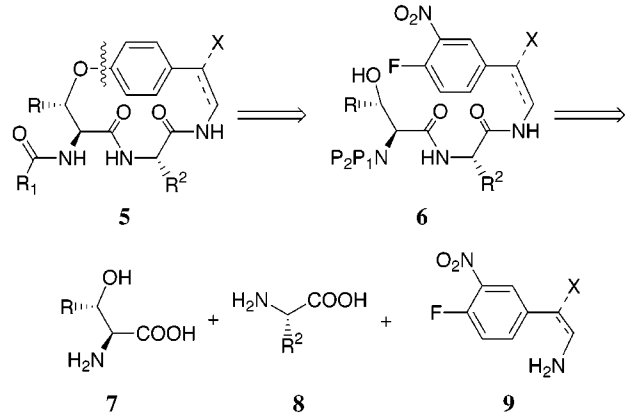
tion via formation of an aryl−alkyl ether bond is not feasible in the presence of various functional groups present in the peptidic precursor.

In connection with our interests in the total synthesis of vancomycin and related antibiotics,[13] we have been working on the intramolecular S_NAr reaction for the construction of macrocycles via formation of an endo aryl−aryl ether bond.[14−17] This cycloetherification has since been demonstrated to be a powerful methodology for the synthesis of complex molecules.[18] We have attributed the success of this remarkable cycloetherification to an intramolecular recognition phenomenon that favors a folded conformer conducive to cyclization.[19,20] Several structural elements found in our previously studied substrates

Scheme 1



could indeed help their preorganization[21] via possible intramolecular attractive forces such as $\pi-\pi$ stacking,[22] formation of a charge-transfer complex,[23] backbone H-bonding,[24] and electrostatic interactions.[25] To evaluate the influence of a $\pi-\pi$ interaction on the outcome of cyclization and to further expand the generality of this methodology, we were interested in investigating the cyclization involving an alcohol (alkoxide) as an internal nucleophile instead of a phenoxide. The cyclopeptide alkaloids were selected as synthetic targets for this purpose. A unified synthetic scheme featuring a key cycloetherification of the linear peptide **6** is shown in Scheme 1. Besides a significant methodological issue, the advantages of employing such a strategy are as follows: first, two difficult synthetic steps, aryl−alkyl ether bond formation and macrocyclization, are reduced into a single operation; second, it uses an intact peptidic linear precursor making the strategy more convergent. The 14-membered para cyclophane was chosen since it is more strained and less accessible than the 13-membered meta cyclophane. The successful implementation of this strategy and its application in a total synthesis of sanjoinine G1 are the subjects of the present paper.[26]

Results and Discussion

Model Studies I—Importance of the N-Terminal Protecting Group. To validate the proposed strategy, a model linear dipeptide **13** was synthesized as shown in Scheme 2. Coupling

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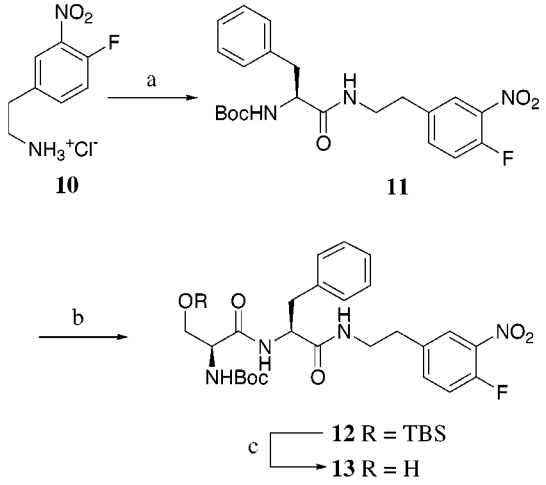
Scheme 2[a]



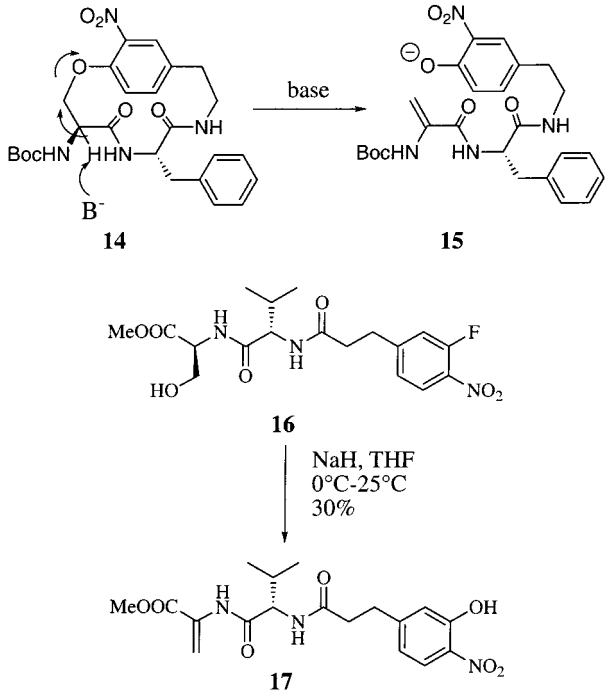
[a] Reagents: (a) *N*-Boc-Phe, Et_3N, EDC, HOBt, 85%; (b) (i) HCl−MeCN, (ii) Et_3N, *N*-Boc-Ser (TBS)OH, EDC, HOBt, 68%; (c) CsF, DMF, 86%.

of 2-(3′-nitro-4′-fluoro) phenylethylamine (**10**)[14a] with *N*-Boc-Phe afforded dipeptide **11**. Removal of *N-tert*-butyloxy carbamate under mild acidic conditions (HCl−MeCN) followed by its coupling with *N*-Boc Ser (OTBS) gave the dipeptide **12** in 68% overall yield. Selective deprotection of silyl ether (CsF, DMF) furnished compound **13**, ready for cyclization studies. Unfortunately, attempted ring closure of **13** under sets of conditions varying solvents (THF, DMF, DMSO), bases (NaH, KHDMS, K_2CO_3, and CsF), temperature, and concentration was uniformly unsuccessful. In most cases, only degradation of the starting material was observed leading to intractable tars.

Knowing the propensity of *N*-Boc Serine derivatives to undergo β-elimination under basic conditions,[27] we surmised that dipeptide **13** may not be the right substrate for the cyclization studies. The reasoning is that the cyclic compound **14**, if produced at all, would be unstable and would decompose to the acyclic compound **15**. This β-elimination process is likely to be facile due to (1) release of ring strain, and (2) the fact that ortho nitro substituted phenol is a good leaving group (Scheme 3). While we were unable to isolate compound **15** at this stage of work, we did verify later that such a degradation process is indeed operating. Thus, treatment of dipeptide **16** with NaH in THF afforded a rather complex reaction mixture from which a dehydroalanine derivative **17** was isolated in 30% yield.[28]

It is reasonable to assume that the suspected β-elimination is initiated by deprotonation of the terminal serine α-CH. Consequently, reducing the thermodynamic and/or kinetic acidity of this proton should help avoid such a process. Since the carboxylic group of serine is engaged within the cyclophane unit, the amino group is the only function that can be manipulated for this purpose. The acidity of the α-CH and hence the rate of the racemization of a given amino acid derivative under basic conditions are highly dependent on the nature of the nitrogen protecting group and are higher when the protected

Scheme 3



nitrogen is less basic.[29] For this reason, cyclization of a dipeptide with a terminal primary amine and a terminal *N*,*N*-dialkylated amino function was next investigated. Indeed, it has been demonstrated that the bulky phenylfluorenyl and trityl protecting groups protect the α-center of amino acids from deprotonation, thus preventing the racemization[30] and β-elimination.[31]

A simultaneous deprotection of *N*-carbamate and *O*-silyl ether of **12** with HCl−MeCN gave amino alcohol **18** (Scheme 4). In principle, cyclization of compound **18** could lead to the formation of two chemically distinct products resulting from O- and/or N-arylation. Because of the hindered rotation around the newly formed C_{sp2}−heteroatom bond and the presence of a nitro group ortho to this linkage, a planar chirality will be created after cyclization. Thus theoretically, four cyclophanes could be produced from **18**. The results of cyclization under various conditions are summarized in Table 1. As it is seen, neither NaH nor K_2CO_3 was able to promote the cyclization in different reaction media. However, when TBAF in THF was used as a base, a mixture of two separable products **19a** and **19b** (one-to-one ratio) was isolated in 65% yield. In terms of the yield, THF was found to be a better solvent than was DMF in this particular case (entries 6 vs 7).[32] Although addition of molecular sieves was beneficial to the cyclization, other additives such as sodium sulfate and cesium carbonate blocked completely the reaction.

The cyclic structure of these two products is readily deduced from both ^1H NMR and mass spectrometry. However, the available spectroscopic data did not allow us to distinguish between the N- and O-cyclized compounds (**19** and **20**,

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(32) In accord with the ionic mechanism of S_NAr, cycloetherification proceeded generally faster in DMF and DMSO than in THF. However, in some cases, THF was found to be a solvent of choice although longer reaction time was required. For examples in the biaryl ether series, see refs 14g and 19b.

Scheme 4

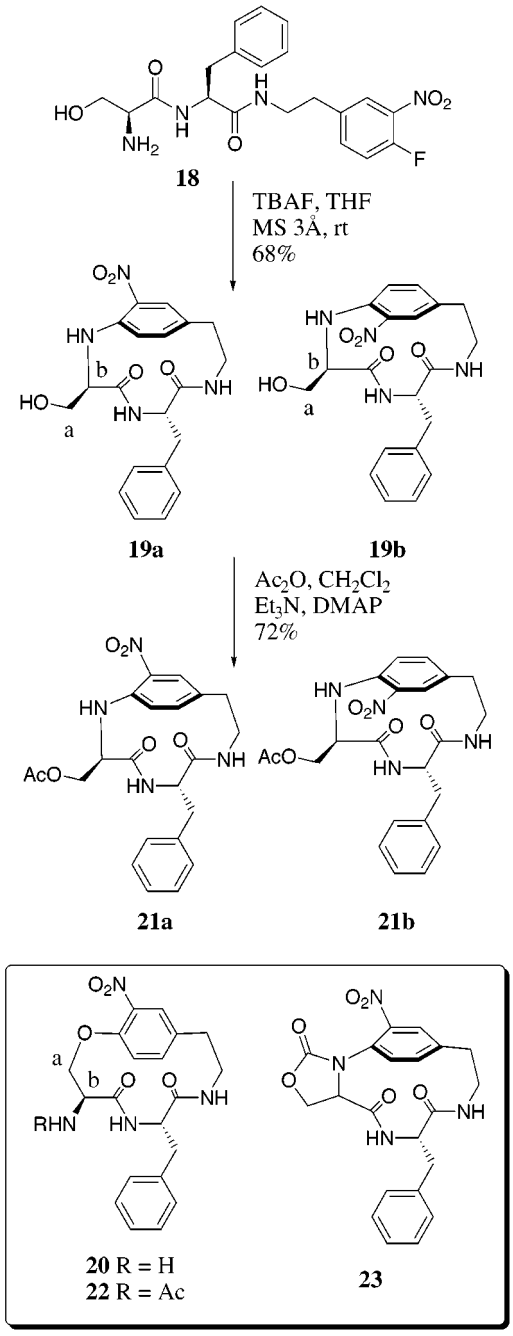


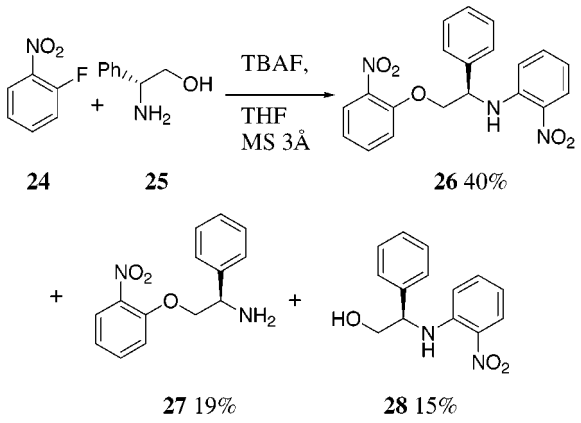
Table 1. Cyclization of **18** to **19**: Survey of Cyclization Conditions[a]

base	additive	solvent	T°C	time (h)	yield (%)
NaH		DMF	20	24	0
NaH		DMF	60	48	0
NaH		THF	20	24	0
K_2CO_3		DMF	60	24	0
K_2CO_3		DMSO	20	24	0
TBAF		THF	20	48	65
TBAF		DMF	20	48	50
TBAF		THF	90	48	0
TBAF	Na_2SO_4	THF	20	48	0
TBAF	Cs_2CO_3	THF	20	48	0
TBAF	3 Å	THF	20	12	68

[a] Five equivalents of base was employed.

respectively, Scheme 4). A chemical transformation was thus carried out to gain more structural information. Acetylation

Scheme 5



(Ac_2O, DMAP, Et_3N, CH_2Cl_2) of individual cyclic compounds **19a** and **19b** gave mono acetylated derivatives whose structures were determined to be the 13-membered cyclophanes **21a** and **21b**, respectively, on the basis of the following facts. First, in the ^1H NMR spectra of cyclophanes **21a** and **21b**, both protons Ha moved to low field while Hb was almost unchanged as compared to their starting materials. If it was **22** resulting from the acylation of the O-cyclized cyclophane **20**, we would expect the low-field shift of proton Hb after N-acylation. Second, the appearance of a strong absorption peak at 1737 and 1749 cm^{-1} in the IR spectra of **21a** and **21b** indicated the presence of an ester rather then an amide bond. Furthermore, treatment of the cyclic compound **19a** with 1,1′-carbonyldiimidazole produced an oxazolidinone **23** which definitively discarded the structure **20** as a primary cyclic compound. From these studies, we concluded that cyclization of **18** produced the two atropisomers of the 13-membered para cyclophanes **19a** and **19b** at the expense of the 14-membered para cyclophane, presumably because the nitrogen nucleophile is more accessible. Attemps to convert the compound **19** into **20** via Smiles rearrangement failed under various basic conditions.

Depending on the reaction conditions, an intermolecular S_NAr reaction between an amino alcohol and a fluoro nitro aromatic compound can produce chemoselectively the N- or O-arylated product. Thus a strong base (NaH) promotes the O-arylation, while a weaker base (e.g., K_2CO_3) favors the N-arylation.[33] In view of the peculiar property of ionic fluoride and its known ability to promote the O-alkylation and O-arylation,[34] the exclusive N-cyclization of **18** was intriguing. To learn whether this chemoselective cyclization is a substrate-controlled or a reagent-controlled process, an intermolecular condensation between 2-fluoro nitrobenzene **24** and (*R*)-phenyl glycinol **25** was performed using TBAF as a base in THF. As shown in Scheme 5, TBAF is capable of promoting both the N- and the O-arylation of amino alcohol. The result of this control experiment clearly indicated that the high chemoselectivity observed in the cyclization of **18** is inherent to this particular substrate and may not be a general phenomenon. The observed shorter distance of $N-C_F$ than that of $O-C_F$ in an energy-minimized conformation may explain in part the observed selectivity.

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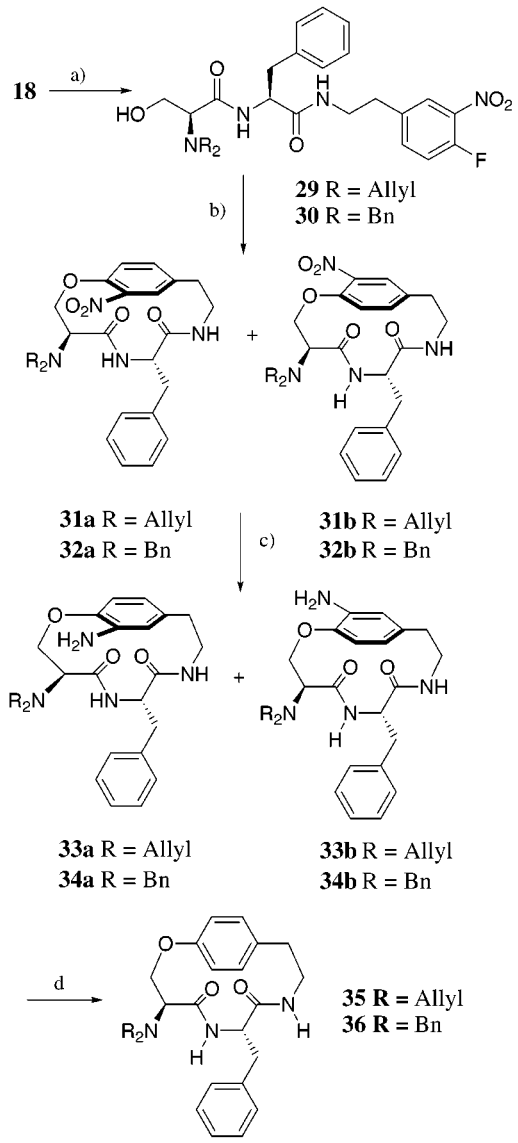
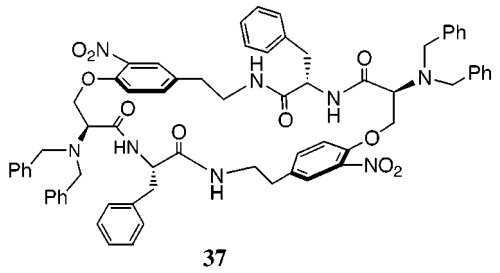
Scheme 6[a]



[a] Reagents and Conditions: (a) THF/DMSO (4/1), allyl bromide, or BnBr, $NaHCO_3$, 80 °C, 70−85%; (b) TBAF, DMF, molecular sieves, room temperature, 4 h, 60−75%; (c) $NaBH_4$, elemental sulfur, THF, reflux, 81%; (d) (i) *t*-BuONO, $BF_3{\cdot}Et_2O$, CH_2Cl_2, −15 °C, (ii) $FeSO_4$, DMF, room temperature, 65−75%.

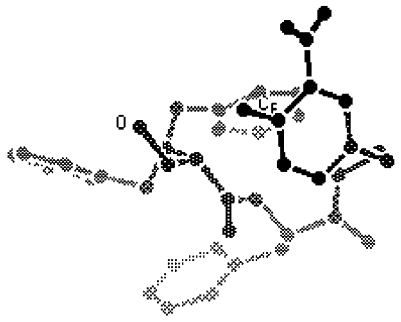
Although cylization of **18** provided the wrong regioisomers, occurrence of such a reaction under defined conditions was encouraging, and we set out to study the cyclization of substrates with a terminal *N*,*N*-dialkyl amino function. Chemoselective *N*,*N*-bisallylation or *N*,*N*-bisbenzylation of **18** in the presence of primary hydroxyl function was realized by using $NaHCO_3$ as a base in mixed solvent (DMSO/THF = 1/4) to afford **29** and **30** in 78% yield (Scheme 6).

When a DMF solution of **29** (0.01 M) was treated with TBAF in the presence of molecular sieves at room temperature for 4 h, a mixture of two cyclized monomers **31a** and **31b** was isolated in 75% overall yield. THF could also be used as solvent for the cyclization; however, a significantly prolonged reaction time (4 days) was required to complete the cyclization. Similar treatment of compound **30** afforded two separable products **32a** (32%) and **32b** (48%), whose structure was assigned as two atropisomers from spectroscopic studies and was confirmed by subsequent chemical transformation. A control experiment



37

Figure 2.



E_1 = -158.13 KJ/Mol (0.739), 2H bond, HO-C_F = 4.677 A

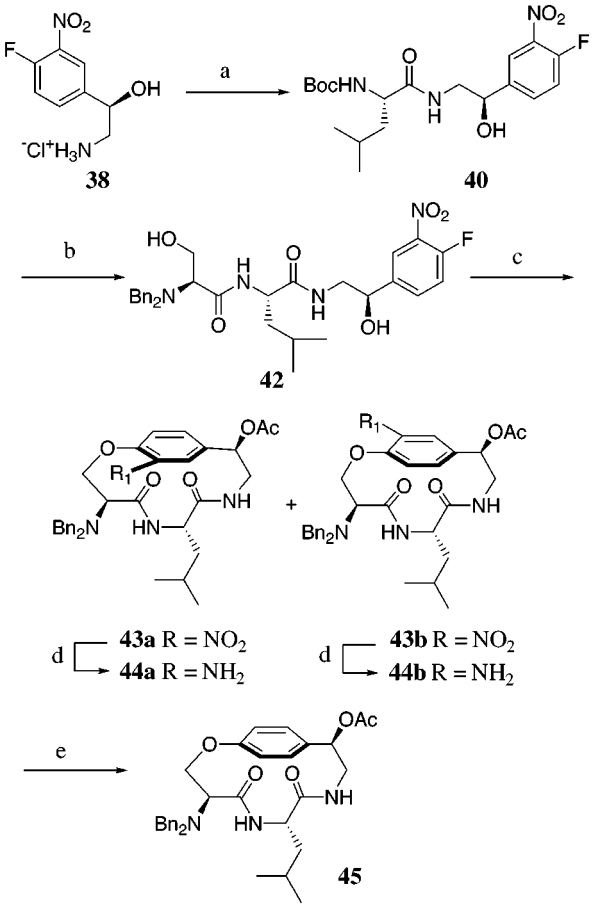
Figure 3.

showed that compounds **32a** and **32b** did not undergo equilibrium under the cyclization conditions, indicating therefore that they are kinetic products. The removal of the nitro group was carried out by a two step sequence. Reduction of a mixture of **31a** and **31b** with sulfurated $NaBH_4$ [35] in THF gave the corresponding amino compounds **33**, and the two atropisomers became separable at this stage by flash chromatography. Diazotization of **33a** and **33b** under Doyle's conditions[36] followed by $FeSO_4$-mediated reduction of the crude diazonium salt[37] gave the desired cyclophane **35** (R = allyl) in 65% overall yield. The same sequence applied to **32a** and **32b** gave the amino compounds **34a** and **34b** and then the reduced cyclophane **36** (R = Bn) in 67% yield. As is seen in the ^1H NMR spectra of compounds **35** and **36**, the four protons in the para disubstituted benzene ring are chemically inequivalent, each being an apparent doublet of doublet. Such a splitting pattern is indicative of the severe ring strain, which hindered the free rotation around aryl−alkyl ether bond.

The key S_NAr-based cyclization was routinely carried out in 0.01 M DMF. A higher dilution was unnecessary; however, variable amounts of cyclic dimer **37** (Figure 2) were observed when the cycloetherification of **30** was performed at a concentration of 0.05 M under otherwise identical conditions. To gain information regarding the solution conformations of the cyclization precursor, we carried out a computational simulation (macromodel, Batchmin version 3.5 a, OPLS force field,[38] water set). The calculated lowest energy conformer of **30** (Figure 3) has a bent orientation placing the two reactive sites (HO and C_F) within a distance of 4.67 Å. Such a "near attack conformation"[39] should thus reduce the entropy loss of the cyclization

(35) Lalancette, J. M.; Frêche, A.; Brindle, J. R.; Laliberté, M. *Synthesis* **1972**, 526−532.
(36) Doyle, M. P.; Bryker, W. J. *J. Org. Chem.* **1979**, *44*, 1572−1574.
(37) Wassmundt, F. W.; Kiesman, W. F. *J. Org. Chem.* **1995**, *60*, 1713−1719.
(38) Jorgensen, W. L.; Tirado-Rivers, J. *J. Am. Chem. Soc.* **1988**, *110*, 1657−1666.
(39) Bruice, T. C.; Lightstone, F. C. *Acc. Chem. Res.* **1999**, *32*, 127−136.

Scheme 7[a]



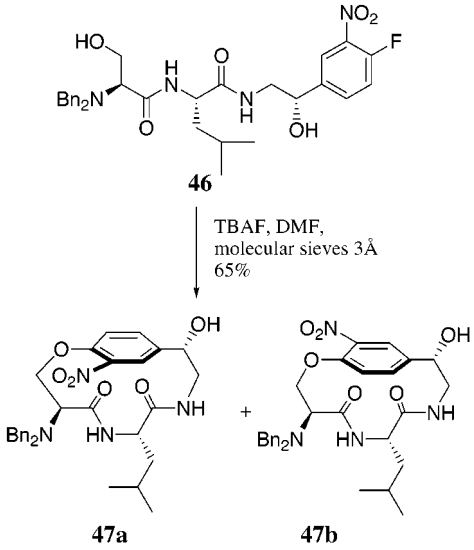
[a] Reagents and Conditions: (a) L-*N*-Boc Leu (**39**), EDC, HOBt, 92%; (b) (i) HCl−MeCN (15% v/v), (ii) EDC, HOBt, L-*N*,*N*-dibenzyl Ser (**41**), 80%; (c) (i) TBAF, DMF, molecular sieves 3 Å, (ii) Ac_2O, Et_3N, DMAP, 70%; (d) $NaBH_4$, elemental sulfur; (e) (i) *t*-BuONO, BF_3·OEt_2, (ii) Fe, $FeSO_4$, DMF, 65%.

process, resulting in a low activation energy for cyclization. Besides protecting the α-CH of serine from deprotonation, it is also conceivable that the presence of the bulky bisalkylated amino substituent may impart an element akin to a *gem*-dimethyl effect[40] which preorganizes the substrate into a productive conformation.

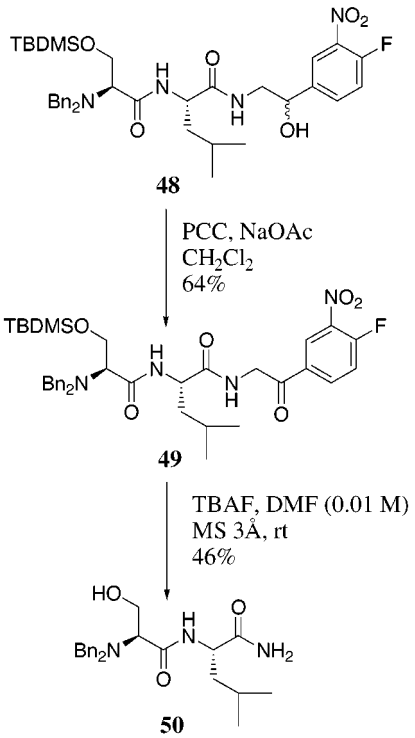
To further validate the potential of this strategy in the synthesis of a cyclopeptide alkaloid, linear peptide **42** incorporating an optically pure (*R*)-2-amino-1-(4′-fluoro-3′-nitro) ethanol[41] was synthesized (Scheme 7). Treatment of a DMF solution of **42** (0.01 M) with TBAF in the presence of molecular sieves (3 Å) at room temperature gave two separable atropisomers **43a** (35%) and **43b** (35%) after acylation. Reductive removal of a nitro function provided then the cyclophane **45** in 65% overall yield. Thus, the presence of a hydroxyphenethylamine unit did not affect the efficiency of the cycloetherification reaction.

To verify whether the stereochemistry of the chiral secondary benzyl alcohol can exert any influence on the macrocyclization reaction, compound **46**, an epimer of **42**, was synthesized starting from (*S*)-2-amino-1-(4′-fluoro-3′-nitro) ethanol (Scheme 8). Cyclization of **46** under the standard conditions (TBAF, DMF, MS 3 Å) provided two separable cyclophanes **47a** and **47b** in 65% yield. The same efficiency observed between the cyclization of **42** and **46** indicated that the S_NAr-based cycloetherification was insensitive to the chirality of the tether chain, expanding further its general applicability in organic synthesis.

Scheme 8



Scheme 9

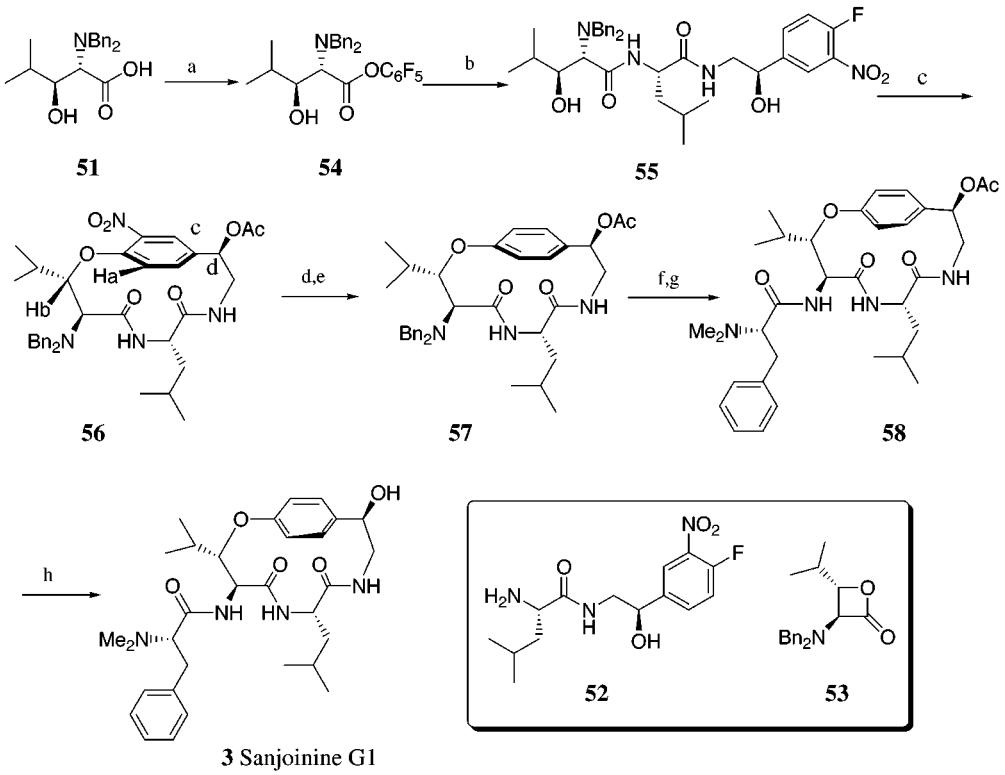


Overall, by simply tuning the N-protective group from *N*-*tert*-butyloxycarbamate to *N*,*N*-dialkyl amino function, we were able to bypass the otherwise dead-end of a synthetic strategy.[42]

Model Studies II—Activation Level of Aromatic Ring for S_NAr Reaction. The presence of electron-withdrawing groups facilitates the nucleophilic aromatic substitution.[43] We thus reasoned that introduction of a carbonyl function at the benzylic position of **30** should further improve the reaction outcome. If

(40) Jung, M. E.; Gervay, J. *Tetrahedron Lett.* **1988**, *29*, 2429−2432.
(41) Laïb, T.; Ouazzani, J.; Zhu, J. *Tetrahedron: Asymmetry* **1998**, *9*, 169−178.
(42) For an interesting review, see: Sierra, M. A.; Torre, M. C. *Angew. Chem., Int. Ed.* **2000**, *39*, 1538−1559.

Scheme 10[a]



[a] Reagents and Conditions: (a) EDC, C_6F_5OH, CH_2Cl_2; (b) DMF, **50**, 60 °C, 75%; (c) TBAF, DMSO, 85 °C, then Ac_2O, Et_3N, DMAP, CH_2Cl_2, 45%; (d) $SnCl_2$, DMF, 60 °C; (e) $NaNO_2$, H_3PO_2, Cu_2O, THF-H_2O, 73%; (f) $Pd(OH)_2$, THF-*t*-BuOH, quantitative; (g) L-*N*,*N*-dimethyl phenylalanine, EDC, HOBt; (h) K_2CO_3, MeOH-H_2O, 85%.

cyclization occurred, the reagent-controlled reduction of the carbonyl function[44] would provide directly the core structure of natural product with a stereochemically defined hydroxyphenethylamine unit.[9g]

A PCC-mediated oxidation of **48** in buffered dichloromethane solution provided linear peptide **49** (Scheme 9). Surprisingly, treatment of **49** under conditions identical to those established earlier provided the dipeptide amide **50** as the only isolable compound in 46% yield. The structure of **50** was fully determined by comparison with an authentic sample obtained by amidation of the corresponding dipeptide acid. The fact that the C-terminal of compound **50** was an amide instead of an acid eliminated the simple hydrolysis mechanism and implied a rather complex reaction manifold. Failure to isolate the other part of the degraded molecule prohibited any meaningful mechanistic speculation. Nevertheless, oxidation of the carbon α to the ketone function by adventitious oxygen followed by fragmentation of the so-produced hemiaminal could be one of the possible reaction pathways leading to **50**. Other conditions varying the base and the solvent were briefly surveyed for the cyclization of **49**. Unfortunately, none of them gave the expected cyclophane. In view of the successful cyclization of compound **42**, we turned our attention on its application in the total synthesis of natural products.

Total Synthesis of Sanjoinine G1. Sanjoinine G1 (**3**) (Figure 1) has recently been isolated from sanjoin (seed of *Zizyphus vulgaris*) and was shown to possess an interesting sedative effect.[5] In fact, sanjoin has been frequently used in oriental medicine as an important and reliable hypnotic or sedative agent for the treatment of insomnia. Two total syntheses have been accomplished by Han[11a] and Joullié[9f,h] employing a key macrolactamization reaction.

Our synthesis of sanjoinine G1 was shown in Scheme 10. The (2*S*,3*S*)-*N*,*N*-dibenzyl hydroxyleucine **51** was prepared from (2*S*,3*S*)-hydroxyleucine,[45] by a sequence of esterification, *N*,*N*-bisbenzylation, and saponification under classic conditions in excellent overall yield. The coupling of acid **51** with amine **52** proved to be more difficult than originally anticipated. Attempted one pot activation/coupling using various coupling reagents under diverse conditions provided the desired peptide in low yield. The β-lactone **53** resulting from the intramolecular attack of the β-hydroxyl group onto the activated carboxylic function was found to be the major product in most of the cases. Eventually, the best condition found was activation of the carboxylic acid as its pentafluorophenol ester **54**.[46] Heating a mixture of **52** and **54** in DMF at 60 °C then reproducibly provided the dipeptide **55** in higher than 75% yield. Activation of **51** as its acyl fluoride[47] followed by coupling with **52** gave a lower yield of **55**.

Cyclization of **55** was best realized in DMSO in the presence of TBAF and 3 Å molecular sieves at 85 °C. Under these conditions, the desired 14-membered ansa cyclophane **56** was obtained in 45% yield after O-acylation. The reacting secondary alcohol in compound **55** is highly hindered since it is flanked

(43) (a) Terrier, F. *Nucleophilic Aromatic Displacement: The Role of the Nitro Group*; VCH: New York, 1991; Chapter 1. (b) Paradisi, C. Arene Substitution via Nucleophilic Addition to Electron Deficient Arenes. *Comprehensive Organic Synthesis*; Pergamon Press: Oxford, 1991; Vol. 4, pp 423−450. (c) Vlasov, V. M. *J. Fluorine Chem.* **1993**, *61*, 193−216.
(44) Cyclopeptide alkaloid with a ketone function has been isolated, see: Pais, M.; Marchand, J.; Ratle, G.; Jarreau, F.-X. *Bull. Soc. Chim. Fr.* **1968**, 2979−2984.
(45) Laïb, T.; Chastanet, J.; Zhu, J. *J. Org. Chem.* **1998**, *63*, 1709−1713.
(46) Kisfaludy, L.; Schön, I. *Synthesis* **1983**, 325−327.
(47) Carpino, L.; Sadet-Aalaee, D.; Chao, H. G.; DeSelms, R. H. *J. Am. Chem. Soc.* **1990**, *112*, 9651−9652.

by a bulky isopropyl and a *N*,*N*-dibenzylamino group at the adjacent positions. This unfavorable steric effect may account for the moderate cyclization yield. It is interesting to note that only one atropisomer was isolated from the reaction mixture. From detailed NMR studies, especially the observation of the NOE cross-peak of protons Ha and Hb, a *M* configuration was assigned for the newly created planar chirality.[48]

Reduction of nitro to amino group ($SnCl_2$, DMF) followed by one-pot reductive-deamination provided compound **57**. Lalancette's conditions ($NaBH_4$, S_8) were found to be inefficient for the reduction of nitro in contrast to our model studies. Hydrogenolysis of the *N*-benzyl group was realized using Pearlman's catalyst in THF-*t*-BuOH to provide **58** in quantitative yield. When hydrogenolysis was carried out in methanol or ethanol, partial transesterification occurred to give a deacetylated compound, complicating thus the synthetic operations. The benzylic acetoxy group was perfectly stable under both the tin chloride (acidic)-mediated reduction of nitro group and the hydrogenolysis conditions. Examination of a Dreiding model as well as molecular modeling studies showed that the σ bond C_c-C_d in macrocycles lies out of the plan defined by the aromatic ring. Such an unusual bond organization, inherent to the strained 14-membered para cyclophane, led to the loss of benzylic carbon character of C_d, accounting for the stability of the C_d−oxygen bond under the reducing conditions. Finally, coupling of the crude hydrogenolysis product with L-*N*,*N*-dimethyl phenylalanine followed by saponification gave sanjoinine G1 (**3**) in 85% overall yield whose spectroscopic data is in all respect identical to those reported in the literature.

In conclusion, we have devised and executed an efficient and unified synthetic strategy to the family of cyclopeptide alkaloids. This novel synthesis features a key intramolecular S_NAr reaction for the formation of an aryl−alkyl ether bond under mild conditions. Thus treatment of linear peptide (generic structure **6**, Scheme 1) with TBAF in polar aprotic solvents (THF, DMF, or DMSO) provided the 14-membered para cyclophane in good yield. The importance of the N-terminal protective group in the realization of such a strategy has been demonstrated. Indeed, cyclization of peptide **13** containing a terminal *N*-Boc serine residue afforded intractable tars, while that incorporating a *N*,*N*-dialkyl serine terminal (**29**, **30**, **42**, **46**, and **55**) cyclized to provide the desired macrocycles. Reducing the kinetic/thermodynamic acidity of the α-CH proton of serine, thus protecting the strained para cyclophane from the destructive β-elimination, has been the rationale behind such a productive N-protective group tuning. The overall synthetic scheme is highly convergent since only two conventional couplings are required to reach the cyclization precursor. The nitro group, after serving as an activating group for the S_NAr-based cycloetherification, can be efficiently removed according to literature procedures. From the appropriate amino acid constituents, the natural sanjoinine G1 has been synthesized in seven steps with 21% overall yield which is superior to previous syntheses.

(48) A *P* configuration was erroneously assigned in our preliminary communication (ref 26b).

Experimental Section

Full experimental details and compound characterizations are provided in the Supporting Information.

Acknowledgment. We thank CNRS for support of this research. A doctoral fellowship from "Ligue Nationale Contre le Cancer" to T.T.L. is gratefully acknowledged.

Supporting Information Available: Experimental procedures and spectroscopic and analytical data for all compounds (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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