Generation of Aza-*ortho*-xylylenes via Ring Opening of 2-(2-Acylaminophenyl)aziridines: Application in the Construction of the Communesin Ring System
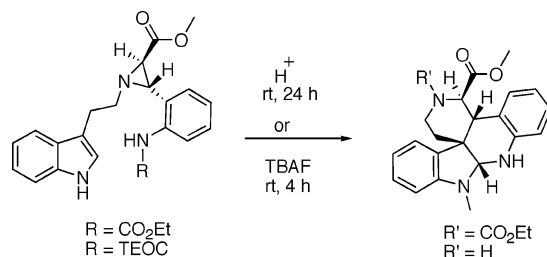
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ABSTRACT

A new protocol for generating aza-*ortho*-xylylenes via acid-catalyzed or fluoride-promoted ring opening of 2-(2-acylaminophenyl)aziridines is described. This methodology has been exploited in the rapid construction of a hexacyclic substructure of communesin B.

The communesins are an emerging class of structurally intriguing and biologically active *Penicillium* metabolites.[1] Communesin B (Scheme 1) exhibits the most interesting biological profile and is moderately cytotoxic against P-388 (ED_{50} = 0.88 μM),[1b] LoVo (MIC = 3.9 μM),[1b] and KB (MIC = 8.8 μM)[1a] cells whose mechanism of action may involve the disruption of microfilaments.[1b] Therefore, it is surprising that communesin B has only recently elicited the interest of synthetic groups[2] despite its first isolation by Numata in 1993.[1a]

We recently reported a strategy for the construction of the hexacyclic core ring system **5** of communesin B[2b] that featured an intramolecular cycloaddition of a *N*-acyl-aza-*ortho*-xylylene **4** with a tethered indole (Scheme 1). The intermediate **4** was generated via thermolysis of the carbonate derivative **3**, which in turn was readily prepared via aminolysis of the epoxide **2** with the benzazepine **1** (Scheme 1). To elaborate the pyrrolidine ring of communesin B, we had hoped to prepare compound **7** (Scheme 2) whose C(9) ester substituent could be converted to several diazo compounds for the planned C−H insertion reactions at C(8).

(1) (a) Communesins A and B: Numata, A.; Takahashi, C.; Ito, Y.; Takada, T.; Kawai, K.; Usami, Y.; Matsumura, E.; Imachi, M.; Ito, T.; Hasegawa, T. *Tetrahedron Lett.* **1993**, *34*, 2355. (b) Communesin B (erroneously assigned to be nomofungin): Ratnayake, A. S.; Yoshida, W. Y.; Mooberry, S. L.; Hemscheidt, T. K. *J. Org. Chem.* **2001**, *66*, 8717. (c) Ratnayake, A. S.; Yoshida, W. Y.; Mooberry, S. L.; Hemscheidt, T. K. *J. Org. Chem.* **2003**, *68*, 1640. (d) Communesins B, C, D, and E: Jadulco, R.; Edrada, R. A.; Ebel, R.; Berg, A.; Schaumann, K.; Wray, V.; Steube, K.; Proksch, P. *J. Nat. Prod.* **2004**, *67*, 78. (e) Hayashi, H.; Matsumoto, H.; Akiyama, K. *Biosci. Biotechnol. Biochem.* **2004**, *68*, 753. (f) Communesins G and H: Dalsgaard, P. W.; Blunt, J. W.; Munro, M. H. G.; Frisvad, J. C.; Christopherson, C. *J. Nat. Prod.* **2005**, *68*, 258.

(2) (a) May, J. A.; Zeiden, R. K.; Stoltz, B. M. *Tetrahedron Lett.* **2003**, *44*, 1203. (b) Crawley, S. L.; Funk, R. L. *Org. Lett.* **2003**, *5*, 3169. (c) May, J. A.; Stoltz, B. *Tetrahedron* **2006**, 62, 5262. (d) Yang, J.; Song, H.; Xiao, S.; Wang, J.; Qin, Y. *Org. Lett.* **2006**, *8*, 2187.
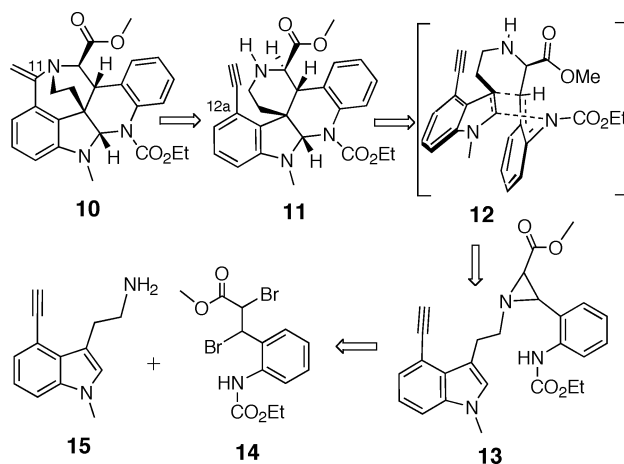
Scheme 1

communesin B
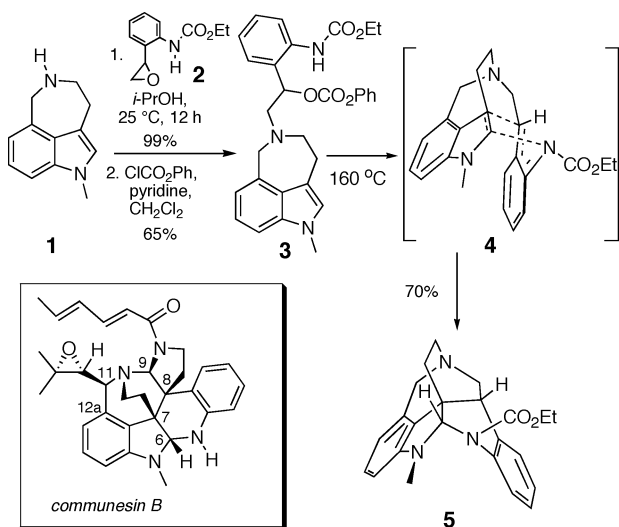
Accordingly, we examined the aminolysis of epoxide **8** with the benzazepine **1**. Unfortunately, we were unable to obtain any of the desired alcohol **9** using a variety of reaction conditions.[3]

Scheme 2
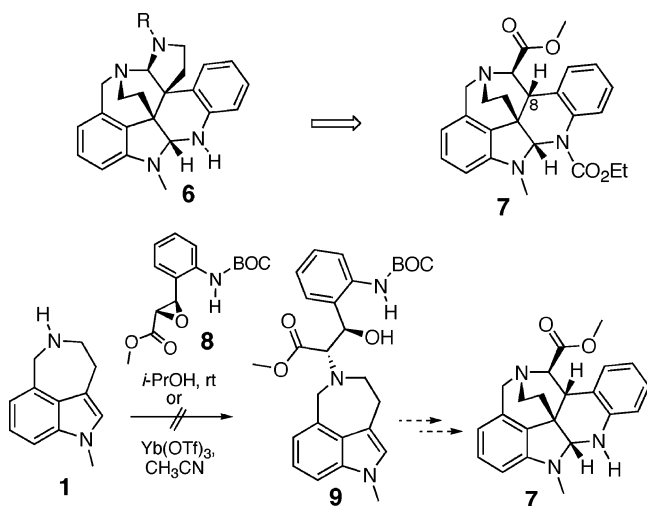
In view of these difficulties, we decided to investigate a synthesis that is more closely related to possible biosynthetic pathways.[2a,c,4] Specifically, the synthesis would begin with a tryptamine derivative thereby necessitating elaboration of the seven-membered ring later in the synthetic sequence (Scheme 3). One advantage of this redesigned route is that

(3) (a) Fujiwara, M.; Imada, M.; Baba, A.; Matsuda, H. *Tetrahedron Lett.* **1989**, *30*, 739. (b) Chini, M.; Crotti, P.; Favero, L.; Macchia, F.; Pineschi, M. *Tetrahedron Lett.* **1994**, *35*, 433. (c) Kotsuki, H.; Shimanouchi, T.; Teraguchi, M.; Kataoka, M.; Tatsukawa, A.; Nishizawa, H. *Chem. Lett.* **1994**, 2159. (d) Meguro, M.; Asao, N.; Yamamoto, Y. *J. Chem. Soc., Perkin Trans. 1* **1994**, 2597. (e) Chakraborti, A. K.; Kondaskar, A. *Tetrahedron Lett.* **2003**, *44*, 8315 and references therein.

Scheme 3

the anticipated facile ring closure of the piperidine ring on the acetylene moiety of pentacycle **11** would provide alkene **10**, a handle for the introduction of the C(11) epoxide substituent. It seemed likely that the intramolecular cycloaddition of the *N*-acyl-aza-*ortho*-xylylene would also proceed through the endo transition state **12** with the ester substituent occupying a position on the convex face.[2b] However, we were concerned about the ramifications of the C(12a) substituent which emerges in a highly congested environment, hence the choice of the compact ethynyl group. Moreover, it was anticipated that the primary amine of indole **15**, vis-à-vis the secondary amine of benzazepine **1**, would allow the efficient assembly of various aza-*ortho*-xylylene precursors. In particular, we were intrigued by the prospect of preparing the aziridine **13** by sequential substitution reactions of dibromide **14** with tryptamine **15** for the purpose of examining its acid- or base-induced ring opening as a means for generating the desired *N*-acyl-aza-*ortho*-xylylene **12**.[5]

We began this investigation by preparing an aziridine that lacked the potentially problematic C(12a) ethynyl substituent (Scheme 4). Thus, alkylation of 1-methyltryptamine with the dibromide **14** provided the trans aziridine **16** in good yield. The stereochemistry of the aziridine was assigned as trans based upon the observed vicinal coupling constant of 2.8 Hz. This value is quite similar to the vicinal coupling constants reported for related trans aziridines and is smaller than the coupling constant that would be expected for the cis diastereomer (6–7 Hz).[6]

We could now evaluate whether protonation of the aziridine **16** would lead to its ring opening and afford the

(4) (a) Fuchs, J. R.; Funk, R. L. *J. Am. Chem. Soc.* **2004**, *126*, 5068. For labeling studies consistent with the tryptamine dimerization pathway previously proposed for the calycanthaceous alkaloids, see: (b) Wigley, L. J.; Mantle, P. G.; Perry, D. A. *Phytochemistry* **2006**, *67*, 561. For seminal examples of proposed calycanthaceous alkaloid biosynthesis, see: (c) Woodward, R. B.; Yang, N. C.; Katz, T. J. *Proc. Chem. Soc.* **1960**, 76. (d) Robinson, R.; Teuber, H. J. *Chem. Ind.* **1954**, 783.

(5) For a review on the synthesis and applications of aza-*ortho*-xylylenes, see: Wojciechowski, K. *Eur. J. Org. Chem.* **2001**, 3587.

(6) For similar aziridine syntheses, see: (a) Ploux, O.; Caruso, M.; Chassaing, G.; Marquet, A. *J. Org. Chem.* **1988**, *53*, 3154. (b) Tokés, A.; Likei, G.; Janzsó, G. *Synth. Commun.* **1990**, *20*, 1905. (c) Davoli, P.; Forni, A.; Moretti, I.; Prati, F.; Torre, G. *Tetrahedron* **2001**, *57*, 1801. (d) Comstock, L. R.; Rajski, S. R. *Tetrahedron* **2002**, *58*, 6019.

Scheme 4

Scheme 4
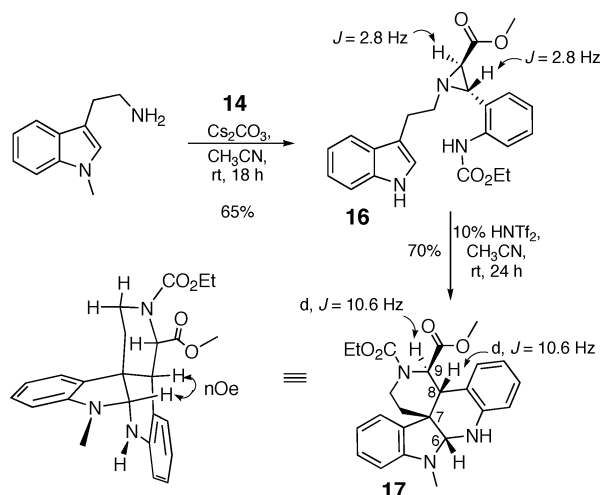
key aza-*ortho*-xylylene intermediate. Brønsted acids possessing nonnucleophilic counterions were first investigated because they would be less prone to undergo intermolecular nucleophilic ring opening of the aziridine.[7] The best results were obtained when bis[(trifluoromethyl)sulfonyl]imide (HNTf$_2$)[8] was employed. Thus, treatment of aziridine **16** at room temperature with HNTf$_2$ provided the cycloadduct **17** whose structure was assigned upon the basis of ^{1}H NMR spectral data. In particular, both the C(8) and C(9) proton resonances appeared as doublets with a large trans coupling constant indicative of a diaxial relationship of these two protons. The alternative exo cycloadduct would be expected to have a much smaller (axial, equatorial) vicinal coupling constant. Moreover, the C(6) aminal proton exhibited a strong nOe with the C(8) methine proton. However, subsequent X-ray crystallographic analysis of carbamate **17** proved to be even more informative (Figure 1). Although the stereo-
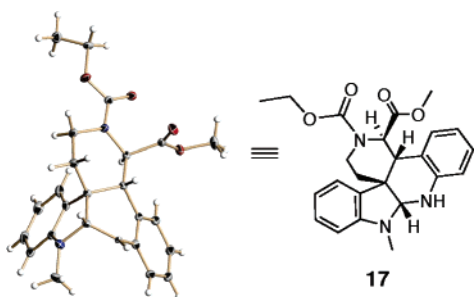
**Figure 1.** X-ray structure of cycloadduct **17**.

chemical assignment was confirmed, we were surprised to discover that the ethoxycarbonyl had migrated to the aziridine nitrogen.

(7) For a review, see: Hu, X. E. *Tetrahedron* **2004**, *60*, 2701.

(8) For recent synthetic applications of HNTf$_2$, see: (a) Kuhnert, N.; Peverley, J.; Robertson, J. *Tetrahedron Lett.* **1998**, *39*, 3215. (b) Zhang, L.; Kozmin, S. A. *J. Am. Chem. Soc.* **2004**, *126*, 10204.

It seemed highly unlikely that the acyl transfer took place following the cycloaddition because we had previously learned that much more vigorous conditions were required for the removal of the robust carbamate functionality present in our initial cycloadduct **5** (KOH, NH$_2$NH$_2$, 150 °C).[2b] Therefore, the more likely scenario is that acyl transfer precedes the cycloaddition and, in fact, is responsible for the generation of the aza-*ortho*-xylylene **20**. A possible mechanism is outlined in Scheme 5. Thus, acid-promoted

Scheme 5

Scheme 5
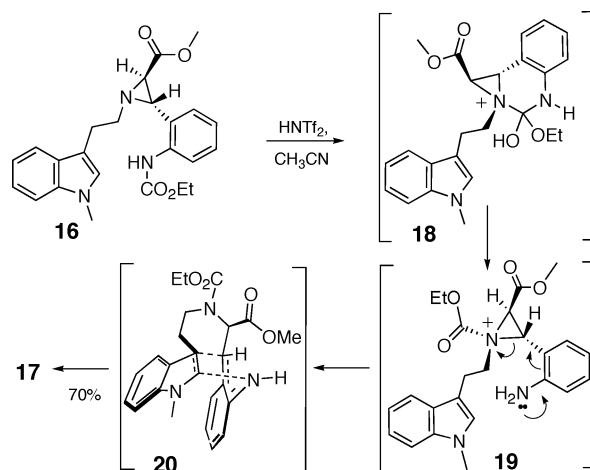
cyclization of the aziridine with the proximate carbamate moiety would afford the aziridinium ion **18** that could undergo proton transfer and ring opening of the six-membered ring to the *N*-acylaziridinium ion **19**,[9] the actual species that triggers ring opening of the aziridine en route to aza-*ortho*-xylylene and thence cycloadduct **17**.

Although this result was intriguing, it was unfortunate in the sense that it is preferable to have the piperidine nitrogen of **17** unprotected at this stage of the synthesis to investigate its closure with a C(12a) ethynyl substituent (vide supra). A possible solution to this problem would be to simultaneously remove the carbamate functionality while generating the aza-*ortho*-xylylene. Some guidance could be derived from the work of Saegusa and Ito who demonstrated that aza-*ortho*-xylylenes could be generated by fluoride-promoted 1,4-elimination of trimethylamine from *ortho*-[*N*-alkyl-*N*-(trimethylsilyl)amino]benzyl trimethylammonium salts.[10] Accordingly, the TEOC carbamate **21** (Scheme 6) was prepared from 1-methyltryptamine and the TEOC analogue of dibromide **14**. We were pleased to discover that treatment of the carbamate **21** with 4 equiv of TBAF effected a smooth conversion to the cycloadduct **22**, presumably via a pathway involving decarboxylative ring opening of aziridine **23** to the aza-*ortho*-xylylene **24**.

(9) *N*-Acylaziridinium ions have been previously observed or proposed; see: (a) Olah, G. E.; Szilagyi, P. J. *J. Am. Chem. Soc.* **1969**, *91*, 2949. (b) Huffman, J. W.; Kamiya, T. *Tetrahedron Lett.* **1966**, *7*, 1857.

(10) (a) Ito, Y.; Nakatsuka, M.; Saegusa, T. *J. Am. Chem. Soc.* **1980**, *102*, 863. (b) Ito, Y.; Nakajo, E.; Saegusa, T. *Synth. Commun.* **1986**, *16*, 1073.

Scheme 6

Scheme 6

TBAF, THF, rt, 4 h

21 → **23** → **24** → **22**

80%
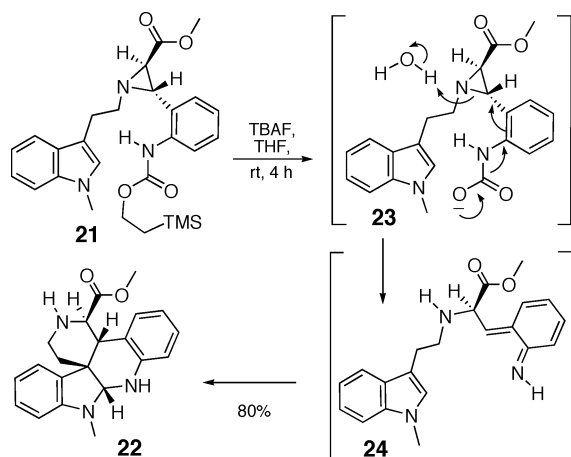
This methodology was now sufficiently developed for its intended application. Our paramount concern was whether the cycloaddition would still take place in the presence of the C(12a) ethynyl substituent. To that end, we prepared carbamate **25** from 4-ethynyl-1-methyltryptamine (**15**)[11] using the same procedure as that employed for carbamate **16**. To our delight, treatment of the aziridine **25** with TBAF cleanly delivered the desired endo cycloadduct **26** (Scheme 7). However, we observed that the cycloadduct **26** underwent
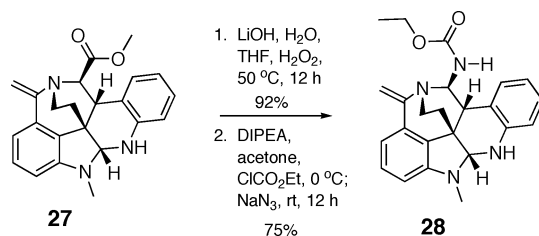
Scheme 7

Scheme 7

TBAF, THF, rt, 4 h

25 → **26**

89%

AuCl(PPh₃), AgOTf, CH₂Cl₂, 40 °C, 12 h,

≡

27
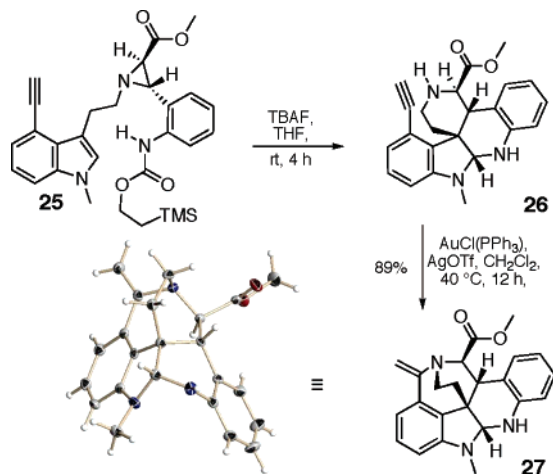
a slow transformation to a secondary product. Consequently, the alkyne **26** was immediately treated with a gold(I) catalyst[12] to provide the enamine **27**[13] via a 7-*exo*-dig ring closure with the nearby piperidine nitrogen. Further exami-

nation of the ¹H NMR spectrum of **26** revealed that the secondary product was in fact enamine **27**, indicating that the intramolecular 7-*exo*-dig closure proceeded spontaneously, albeit slowly, at room temperature. The ease of this cyclization clearly reflects the highly encumbered environment around the C(5) ethynyl substituent. The structure and stereochemistry of this unusual enamine was secured by X-ray crystallographic analysis. Finally, the second aminal functionality was installed by hydrolysis of the ester moiety of enamine **27** (Scheme 8). The resulting acid was converted

Scheme 8

Scheme 8

1. LiOH, H₂O, THF, H₂O₂, 50 °C, 12 h
92%

2. DIPEA, acetone, ClCO₂Et, 0 °C; NaN₃, rt, 12 h
75%

27 → **28**

to the mixed anhydride and then treated with sodium azide to effect a facile Curtius rearrangement to bisaminal **28**.[14]

In conclusion, we have demonstrated that aza-*ortho*-xylylenes can be generated at ambient temperatures via acid- or base-induced cleavage of 2-(2-acylaminophenyl)aziridines and then intercepted with indoles in intramolecular hetero Diels−Alder reactions. The generality of this cascade type of transformation warrants further investigation because both the tetrahydroquinoline and the β-phenethylamine privileged structures are simultaneously constructed. Moreover, this methodology has expedited the construction of a hexacyclic substructure of communesin B that also possesses the bisaminal functionality. Efforts directed toward the completion of the total synthesis are underway and will be reported in due course.

Supporting Information Available: Spectroscopic data and experimental details for the preparation of all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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(11) Prepared in four steps (see Supporting Information) from the known 4-formyl-1-(triisopropylsilyl)gramine; see: Chauder, B.; Larkin, A.; Snieckus, V. *Org. Lett.* **2002**, *4*, 815.

(12) (a) For a related example of a gold-catalyzed intramolecular hydroamination of an arylalkyne, see: Kadzimirsz, D.; Hildebrandt, D.; Merz, K.; Dyker, G. *Chem. Commun.* **2006**, 661. For the cyclization of β-ketoesters with alkynes using this catalyst, see: (b) Kennedy-Smith, J. J.; Staben, S. T.; Toste, F. D. *J. Am. Chem. Soc.* **2004**, *126*, 4526.

(13) For another example of a bridgehead enamine, see: Kirby, A. J.; Komarov, I. V.; Wothers, P. D.; Feeder, N. *Angew. Chem., Int. Ed.* **1998**, *37*, 785.

(14) For the preparation of *N*-acylhemiaminals via Curtius rearrangements, see: (a) Roush, W. R.; Marron, T. G. *Tetrahedron Lett.* **1993**, *34*, 5421. (b) Smith, A. B.; Safonov, I. G.; Corbett, R. M. *J. Am. Chem. Soc.* **2002**, *124*, 11102.