Pergamon

Tetrahedron Letters 42 (2001) 7003–7005

TETRAHEDRON LETTERS

A short synthesis of (1*S*,8a*R*)-1-aminomethyl indolizidine. The heterocyclic core of stelletamides

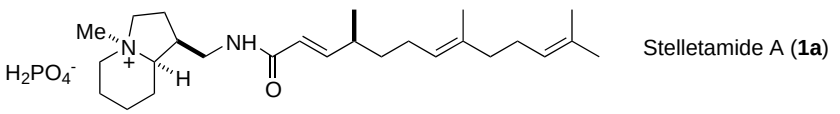
Ronaldo A. Pilli,* Paulo R. Zanotto and Maria Alice Böckelmann

Instituto de Química, UNICAMP, PO Box 6154, 13083-970 Campinas, SP Brazil

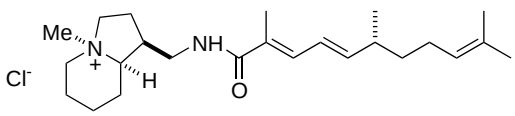
Received 26 February 2001; revised 16 April 2001; accepted 7 August 2001

Abstract—(1*S*,8a*R*)-1-Aminomethyl indolizidine (**2**), the heterocylic core of the stelletamide alkaloids, was prepared in five steps and ca. 20% overall yield starting from oxazolidin-2-one **7**. The key step involved the stereoselective addition of the preformed titanium (IV) enolate from **7** to the *N*-acyliminium ion derived from 2-methoxy piperidine **8b**.

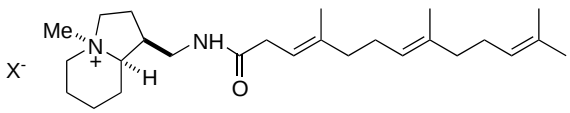
Stelletamides **1a**–**c** are indolizidine alkaloids isolated from marine sponges of the genus *Stelleta* which display antifungal, cytotoxic and RNA-cleaving activities and share (1*S*,8a*R*)-1-aminomethyl indolizidine (**2**) as common architectural motif.[1]



Stelletamide A (**1a**)



Stelletamide B (**1b**)



Stelletamide C (**1c**)

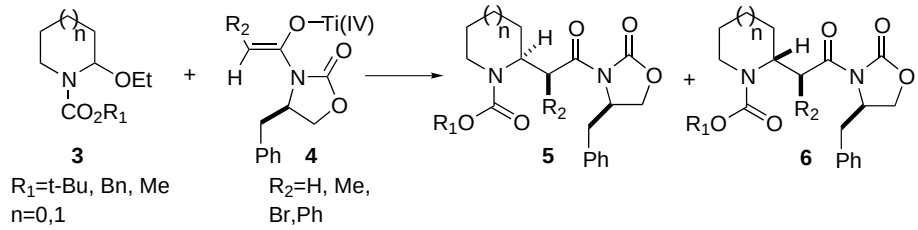
The total synthesis of *ent*-stelletamide A (**1a**) by Whitlock and Carreira[2] established its absolute configuration and featured a highly stereoselective [3+2]cycloaddition reaction of a chiral dipolarophile and (trimethylsilyl)diazomethane as the key step in the construction of the indolizidine core. Recently, Kibayashi and co-workers described the use of a Lewis acid-mediated asymmetric allylation of chiral cyclic *N*-acyl *N*,*O*-acetals in the preparation of indolizidine **2** during the total synthesis of stelletamide B (**1b**).[1c]

Despite the central role played by the early synthetic studies in the elucidation of the absolute stereochemistry of stelletamides **1a**–**c**, the overall length and yield of the synthetic approaches to the 1-aminomethyl indolizidine fragment still leave room for more straightforward strategies.

We have recently described a stereoselective addition of (*Z*)-configured titanium(IV) enolate of chiral *N*-acetyl and *N*-propionyl oxazolidinones to five- and six-membered *N*-acyl iminium ions.[3] The approach turned out to be particularly stereoselective for the addition of the titanium(IV) enolate of *N*-propionyl oxazolidinone to the *N*-acyl iminium ion generated in situ from *N*-Boc 2-ethoxy pyrrolidine whereas no reaction was observed when the six-membered analogue was employed. Upon further examination, we found out that reactivity and diastereoselection were modulated not only by the ring size and the carbamate group, but also by the nature of the acyl group in the oxazolidinone. In fact, 2-substituted piperidines **5** ($n=1$) were formed preferentially from the titanium (IV) enolates **4** derived from *N*-bro-

* Corresponding author. E-mail: pilli@iqm.unicamp.br

0040-4039/01/$ - see front matter
PII: S0040-4039(01)01456-3



moacetyl and *N*-phenylacetyl oxazolidin-2-ones when *N*-carbobenzyloxy or *N*-carbomethoxy 2-ethoxy piperidines **3** were employed.[3–5]

Based on our previous results, we devised a short approach to indolizidine **2** which relies on the addition of the titanium (IV) enolate prepared in situ from (*S*)-*N*-4-chlorobutyryl 2-oxazolidinone (**7**) to six-membered *N*-acyl iminium ions derived from **8a–c**.[6] Upon addition of diisopropylethylamine (DIPEA) to a CH_2Cl_2 soln. of oxazolidinone **7**[7] at −23°C, the reaction mixture developed a purple color characteristic of the corresponding enolate and turned brown after the addition of **8a–c** (Scheme 1).

As observed in our previous studies with less sterically demanding titanium(IV) enolates of *N*-acyl oxazolidinones, the addition of *N*-Boc piperidine **8a** to the preformed enolate soln. did not provide adduct **9a** (oxazolidinone **7** recovered after silica gel chromatography) probably due to the steric crowding provided by the Boc group. However, the use of the less sterically demanding piperidines **8b** (R = Bn) and **8c** (R = Me) circumvented this problem and 2-substituted piperidines **9b** and **9c** were isolated in 62 and 58% yields, respectively, after purification by column chromatography on silica gel.[8]

The (1′*R*,2*R*) configuration of piperidine **9b** established by X-ray diffraction analysis[9] (Fig. 1) revealed the preferential addition of the *Si* face of a chelated *Z*-enolate to the *Si* face of the *N*-acyl iminium ion, in accordance with earlier examples[2,5], and paved the way to its conversion to indolizidine **2**.

Hydrogenolysis of **9b** {$[\alpha]_D$ +85.6 (*c* 2.0, $CHCl_3$)} carried out in ethanol and $Pd(OH)_2$ was followed by tandem intramolecular displacement to provide indolizidine **10** {$[\alpha]_D$ +19.8 (*c* 3.4, $CHCl_3$)} in 73% yield. The recovery of (*S*)-4-benzyl-2-oxazolidinone was efficiently carried out in 72% yield after conversion of indolizidine **10** to the corresponding amide **11**. The addition of LiSEt in THF to the exocyclic carbonyl group[10] provided the corresponding thioester which was treated with aq. NH_4OH and $Hg(OAc)_2$ to yield amide **11** {$[\alpha]_D$ −39.5 (*c* 4.7, $CHCl_3$)} in 56% overall yield,

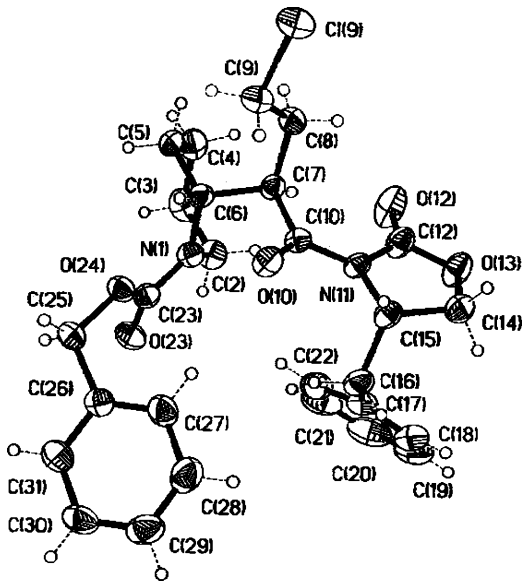
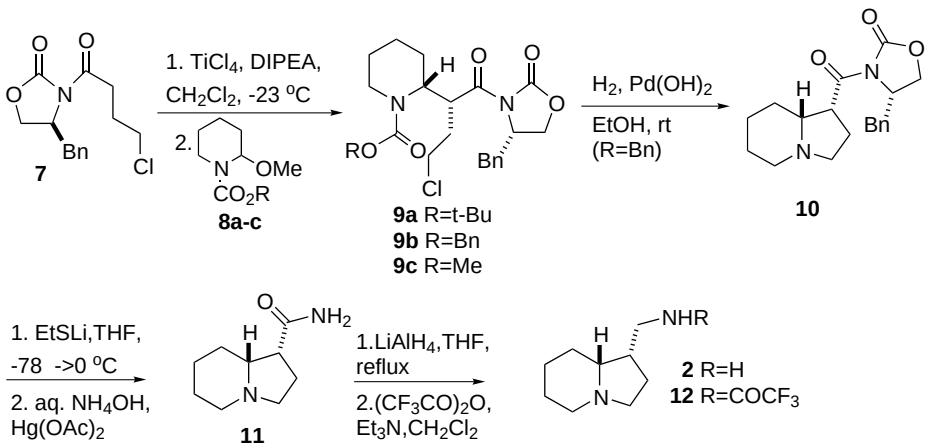


Figure 1.



Scheme 1.

which was employed in the next step without further purification.

The synthesis of (1*S*,8a*R*)-1-aminomethyl indolizidine (**2**)[11] {$[\alpha]_D$ −34.6 (*c* 1.1, $CHCl_3$)} was concluded with $LiAlH_4$ reduction of amide **11** which provided indolizidine **2** in 75% yield as a pale yellow oil.[12] Comparison of the ^1H and ^{13}C NMR spectra and specific optical rotation of trifluoroacetamide **12**{$[\alpha]_D$ −59.0 (*c* 0.32, $CHCl_3$)} with those described by Whitlock and Carreira[2] for *ent*-**12** {$[\alpha]_D$ +60.0 (*c* 0.32, $CHCl_3$)} firmly established the identity of our synthetic (1*S*,8a*R*)-1-aminomethyl indolizidine (**2**) which was obtained in five steps and ca. 20% overall yield from readily available oxazolidinone **7** and 2-methoxy piperidine **8b**.

The significant reduction in the number of steps when compared with the previous approaches[1c,2] together with the potential usefulness of the methodology described here for the construction of analogous motifs found in natural products renders it an important asset on the methods currently available for the construction of chiral bicyclic nitrogen heterocycles.

Acknowledgements

Fapesp for financial support and fellowship to PRZ and CNPq for fellowships to R.A.P. and M.A.B.

References

1. (a) Isolation of stelletamide A: Hirota, H.; Matsunaga, S.; Fusetani, N. *Tetrahedron Lett*. **1990**, *31*, 4163; (b) Isolation of stelletamide B: Shin, J.; Seo, Y.; Cho, K. W.; Rho, J.-R.; Sim, C. J. *J. Nat. Prod*. **1997**, *60*, 611; (c) Revised structure of stelletamide: Yamazaki, N.; Dokoshi, W.; Kibayashi, C. *Org. Lett*. **2001**, *3*, 193; (d) Structure of stelletamide C: Matsunaga, S.; Yamashita, T.; Tsukamto, S.; Fusetani, N. *J. Nat. Prod*. **1999**, *62*, 1202.
2. Whitlock, G. A.; Carreira, E. M. *J. Org. Chem*. **1997**, *62*, 7916.
3. Pilli, R. A.; Alves, C. F.; Böckelmann, M. A.; Nery, J. G.; Mascarenhas, Y. P. *Tetrahedron Lett*. **1999**, *40*, 2891.
4. After our publication appeared, Matsumura and coworkers applied the same methodology for the total synthesis of methyl (*R*,*R*)-phenidate: Matsumura, Y.; Kanda, Y.; Shirai, K.; Onomura, O.; Maki, T. *Tetrahedron* **2000**, *56*, 7411.
5. Pilli, R. A.; Böckelmann, M. A.; Alves, C. F. *J. Braz. Chem. Soc*. **2001**, *12*, 634.
6. Shono, T.; Matsumura, Y.; Tsubata, K. *Org. Synth*. **1985**, *63*, 206.
7. Evans, D. A.; Urpi, F.; Somers, T. C.; Clark, J. S.; Bilodeau, M. T. *J. Am. Chem. Soc*. **1990**, *112*, 8215.
8. The diastereoisomeric ratios were determined to be 5:1 and 3.5:1 for the reaction of **8b** and **8c**, respectively, by ^1H NMR ($CDCl_3$, 328 K) and HPLC analyses of the crude mixtures after filtration over a short pad of silica gel. Although the configuration of the minor product has not being rigorously established in this case, the 2*S*,1′*R* configuration is assumed based on previous examples studied in our group (Ref. 5).
9. We are in debt to Dr. Mathias Noltemeyer Georg-August Universität, Göttingen, Germany for X-ray diffraction analysis of **9b.** Crystallographic data (excluding structure factors) for **9b** in this paper has been deposited with the Cambridge Crystallographic Data Centre as supplementary publication number CCDC 158007. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK [fax: +44 (0) 1223-336033 or e-mail: deposit@ccdc.cam.ac.uk].
10. (a) Damon, R. E.; Coppola, G. M. *Tetrahedron Lett*. **1990**, *31*, 2849; (b) Evans, D. A.; Wu, L. D.; Wiener, J. M.; Johnson, J. S.; Ripin, D. H. B.; Tedrow, J. S. *J. Org. Chem*. **1999**, *64*, 6411.
11. Data for indolizidine (−)-**2**: IR (KBr, film): 3323, 2927, 2852, 2779, 1574; ^1H NMR ($CDCl_3$, 300 MHz): δ 1.10–2.20 (m, 12H), 2.67 (dd, *J* 12.3 and 7.5 Hz, 1H), 2.85 (dd, *J* 12. 3 and 4.5 Hz, 1H), 2.95–3.20 (m, 4H); ^{13}C NMR ($CDCl_3$, 75.5 MHz): δ 24.4, 25.2, 26.4, 26.7, 41.9, 43.4, 53.7, 54.1, 66.5. HRMS (EI, 70 eV) calcd. For $C_9H_{18}N_2$: 154.1470; found: 154.1467.
12. The 1*R* isomer of indolizidine (−)-**2** was isolated{$[\alpha]_D$ +48.5 (*c* 0.83, $CHCl_3$)} in 15% yield, after column chromatography on silica gel. The use of $BH_3{\cdot}Me_2S$ in this step did not avoid formation of the 1*R* isomer and provided lower yields associated with losses during recovery of indolizidine **2** from the intermediate borane–indolizidine complex.