Pergamon

Tetrahedron Letters 39 (1998) 551–554

TETRAHEDRON LETTERS

Synthesis of Cycloisodityrosine Revisited: A Selective Ring Forming Process

Antony Bigot, Jieping Zhu*

Institut de Chimie des Substances Naturelles, CNRS, 91198 Gif-sur-Yvette, France

Received 9 October 1997; accepted 13 November 1997

Abstract: Cycloetherification of dipeptide (L,L) *N*-Boc-(4-fluoro-3-nitro)Phe-Dopa methyl ester (**11**) gave exclusively the (*m,p*)-cyclophane (**14**) at the expense of the 15-membered (*p,p*-)cyclophane (**16**). An efficient synthesis of cycloisodityrosine was consequently developed.

The intramolecular S_NAr based cycloetherification reaction has been developed during the last several years as a powerful synthetic methodology[1-3] and has been employed in the synthesis of a variety of complex biologically important macrocycles with an endo aryl-aryl[1-10] or aryl-alkyl ether[11] linkage. As a continuation of our research program, we became interested in investigating the cyclization of type **A** substrates (Figure 1) in order to study the ring size selectivity during the cyclization (path a *vs* b) and the possible thermoequilibrium of products **B** and **C** via Smiles rearrangement[12]. If the cyclization could be driven, either kinetically or thermodynamically towards the formation of type **B** *meta,para*-cyclophane, then several desirable features would be evident in terms of the synthesis of natural products such as deoxybouvardin (**1**), RA-VII (**2**) and related RA series (Figure 1).[13-17] Firstly, this route would allow the use of commercially available L-dopa instead of side chain selectively protected dopa derivatives for which five steps are required in the till now shortest syntheses.[18] Secondly, 4-fluoro-3-nitrophenylalanine would become the electrophilic partner in S_NAr reaction instead of 3-fluoro-4-nitrophenylalanine, suspected[15] to be responsible for the easy epimerization encountered in the previous S_NAr based synthesis of cycloisodityrosine[14,15] (Scheme 1). Lastly, the access to natural products would be achieved by reductive removal of nitro group, which in our own experience was found to be easier than the corresponding transformation of nitro to hydroxy function, especially in a large scale preparation. The successful implementation of this strategy highlighted by an efficient synthesis of cycloisodityrosine (**3**) is the purpose of this paper.

Linear compounds **10** and **11** (Scheme 2) were prepared following standard procedures. Temporary protection of two hydroxyl groups of L-dopa methyl ester (**7**) as TMS ethers, followed by EDC mediated coupling with 4-fluoro-3-nitrophenylpropionic acid (**8**)[19] or L-*N*-Boc-4-fluoro-3-nitrophenylalanine (**9**)[20] gave, after acidic aqueous work-up, the cyclization precursor (9*S*)-**10** or (9*S*,12*S*)-**11** in more than 85% yield.

The initial cyclization study was carried out with model compound **10** (Scheme 2). When conditions developped for the cyclization of **4** (NaH, THF, 0°C, Scheme 1)[14,15] were applied to **10**, the reaction proceeded as expected to give the two atropodiastereomers of 14-membered *p,m*-cyclophane **13a** and **13b** in reasonable overall yields (55-65%). The formation of 15-membered *p,p*-cyclophane **16** was not observed indicating that neither path b nor Smiles rearrangement (Figure 1) was operating in this case. As matter of fact,

* e-mail: zhu@icsn.cnrs-gif.fr; fax: 33-1-69077247

0040-4039/98/$19.00
PII: S0040-4039(97)10664-5

no Smiles rearrangement was observed when pure cyclophanes **14a** and **14b** were submitted to the cyclization conditions. This result was understandable if one considers the high ring constraints[21] associated with the formation of the *p,p*-cyclophane (**16**). Indeed, Dreiding models showed that compound **16** was too strained to be produced. *A pleasant consequence is that the two otherwise equally reactive hydroxyl functions[22] were successfully differentiated, a phenomenon inherent to the intramolecular process.*[23] A variable amount of cyclic dimer was obtained when the substrate concentration was higher than 0.005 M. The intermolecular S_NAr reaction, slightly more competitive in the cyclization of **10** than in previously studied substrates such as **4**, could be partly explained on statistical grounds as both hydroxyl groups of **11** can participate to an intermolecular process. That compounds **13a** and **13b** were atropodiastereomers was confirmed by independent conversion of the individual macrocycles **13a** and **13b** into the common 14-membered cyclophane **17** via a three step sequence (*vide infra*).

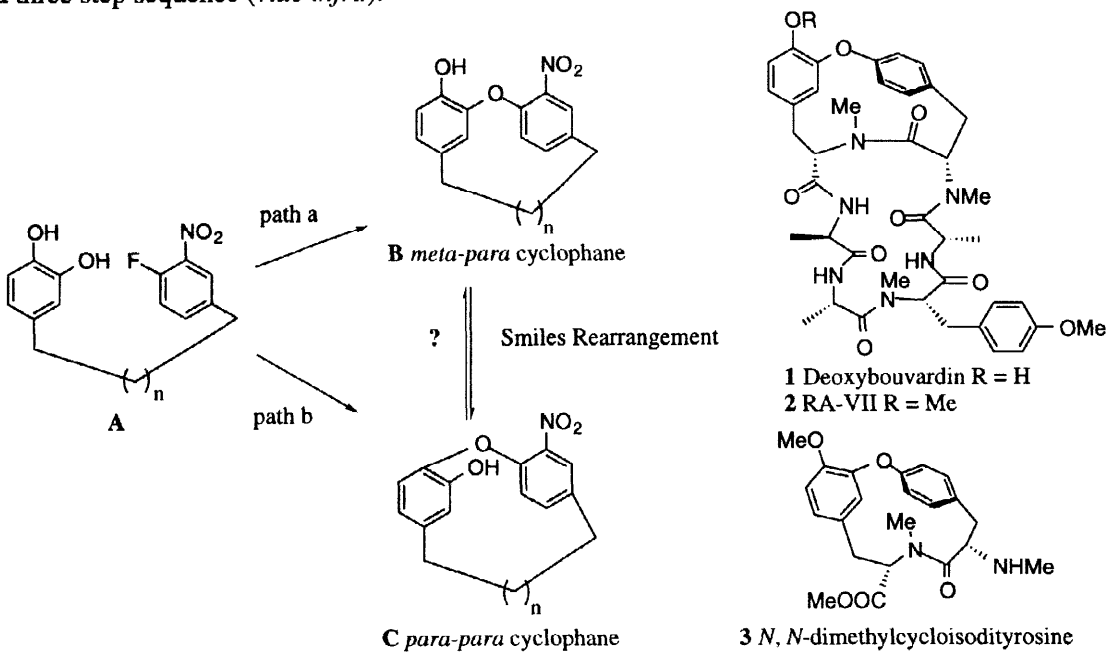
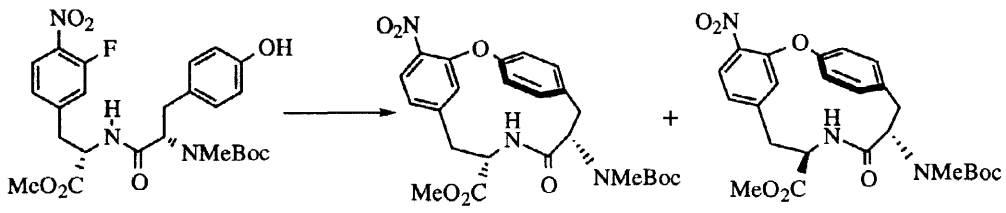


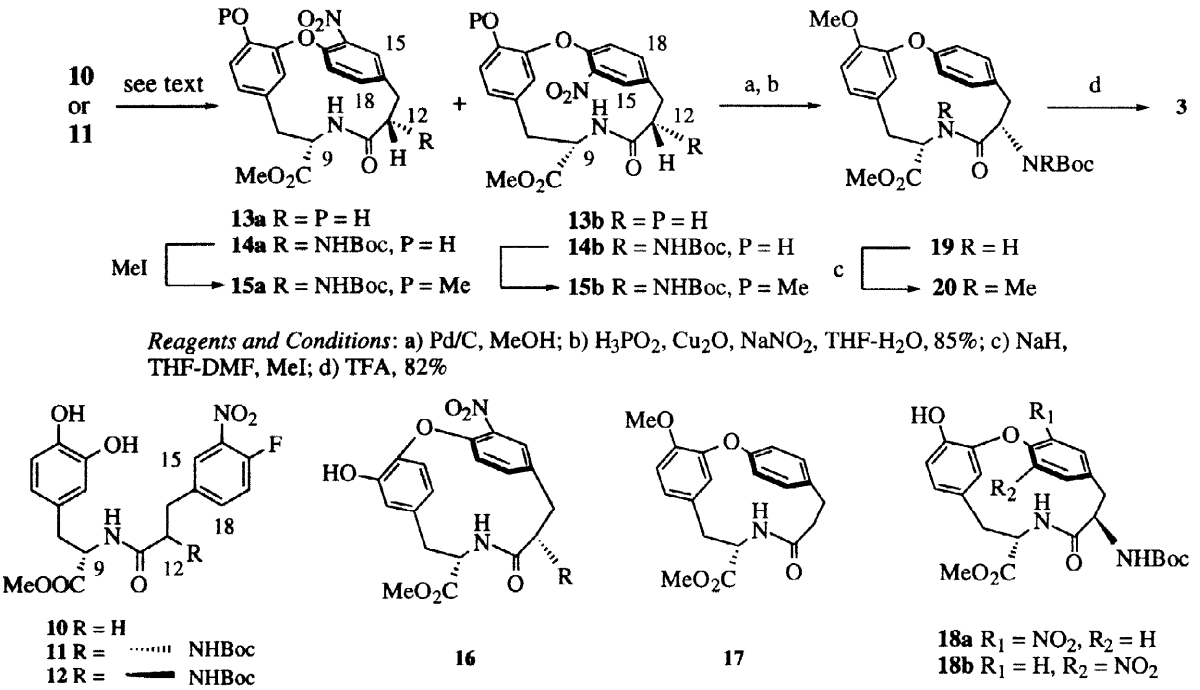
Figure 1



Scheme 1

In contrast, treatment of (9*S*,12*S*)-**11** in THF (0.001 M) with NaH gave no cyclic product and only the starting material was recovered. Thus, a survey of reaction parameters varying the base, the solvent, and the temperature was carried out. It was found that the outcome of the cycloetherification was quite sensitive to the experimental conditions. While no reaction occurred in THF (dielectric constant $\varepsilon = 7.6$), and HMPT ($\varepsilon = 30$)

with either NaH or K_2CO_3 as base, the cyclization proceeded smoothly in more polar aprotic solvents such as DMF ($\varepsilon = 37$), DMSO ($\varepsilon = 47$) being the best in accord with its high dielectric constant. A reasonable reaction rate was observed only at room temperature. At 5°C, the reaction time was substantially prolonged leading to a diminished yield due to partial decompostion of cyclized product. Overall, in the optimal conditions we found (K_2CO_3, DMSO, 0.002M, room temperature), a mixture of cyclic products **14a** and **14b** was obtained in 55-65% isolated yield. While it was difficult to separate the two atropodiastereomers at this stage, the two *O*-methylated products **15a** and **15b**, obtained by treatment of **14a** and **14b** with K_2CO_3 in DMF, were easily separable and their configuration was deduced from NOE experiment. As observed in the vancomycin series,[24] a NOE cross peak between protons H12 and H18 was found in the NOESY spectrum of M atropodiastereoisomer **15a**, while that of H12 and H15 for the P diastereoisomer **15b**.



Scheme 2

The observation that partial degradation of cyclic products **14a** and **14b** occurred during flash chromatography purification and the fact that both cyclization and methylation steps could, *a priori*, be carried out under identical conditions prompted us to examine the possibility of combining these two operations in a one-pot fashion. This tandem reaction sequence was found to be a rewarding experiment as compounds **15a** and **15b** were indeed isolated in greater than 75% yield simply by exposure of a DMSO solution (0.002 M) of dipeptide (9*S*,12*S*)-**11** to K_2CO_3 followed, after 2 h, by addition of MeI (excess) to the reaction mixture.

We have also synthesized compound (9*S*,12*R*)-**12** by reaction of L-dopa (**7**) with D-**9** (Scheme 2). Submitting (9*S*,12*R*)-**12** to identical cycloetherification conditions as described for (9*S*,12*S*)-**11** gave a mixture of two inseparable atropodiastereomers **18a** and **18b** whose physical data were completely different from that of **14a** and **14b** (Scheme 2). This control experiment indicated that the stereochemical integrity of (9*S*,12*S*)-**11** was preserved in both preparation and cyclization steps, in sharp contrast to the easy epimerization encountered with compound (9*S*,12*S*)-**4**. In line with the configurational stability of **14a** and

14b no epimerization occurred by treatment with DBU in THF, conditions known to epimerize **5** (degradation was, however, observed). Overall, these observations provided indirect evidence that the presence of 3-fluoro-4-nitrophenylalanine fragment in compounds **4** and **5** was more or less responsible for their configurational labilty as proposed previously.[15]

The transformation of cyclophane **15a** and **15b** into the desired cycloisodityrosine **3** was straightforward (Scheme 2). Hydrogenation of a mixture of **15a** and **15b** in MeOH in the presence of catalytic amount of Pd/C afforded the amino derivatives which were submitted, without further purification, to *in situ* diazotization and reduction[25] to afford compound **19** {$[\alpha]_D$ = + 56, *c* 0.9, $CHCl_3$; Lit[14]: $[\alpha]_D$ = + 57, *c* 0.6, $CHCl_3$}. *N*-methylation followed by removal of *N*-Boc function from **20** gave then *N,N*-dimethyl cycloisodityrosine **3** whose physical data were identical in all respects with the literature values.[14,15]

In summary, we have described a new route to cycloisodityrosine **3**, an important structural subunit of bouvardin and RA series from readily available starting materials by way of an efficient cycloetherification reaction. The preferential formation of 14-membered *m,p*-cyclophane over the alternative 15-membered *p,p*-cyclophane is a result of an enthalpy controlled process.[26] Further studies to address the generality of this kind of selective ring forming process and its application to natural product synthesis are in progress.

Acknowledgements: A doctoral fellowship from the MRES to A. Bigot are gratefully acknowledged.

References and Notes

1 For a short account, see: Zhu, J. *Synlett* **1997**, 133-144.
2 For a review, see: Burgess, K.; Lim, D.; Martinez, C. I. *Angew. Chem. Int. Ed. Engl.* **1996**, *35*, 1077-1078.
3 For a general review, see: Rao, R. A. V.; Gurjar, M. K.; Reddy, L.; Rao, A. S. *Chem. Rev.*, **1995**, *95*, 2135-2167.
4 Bois-Choussy, M.; Vergne, C.; Neuville, L.; Beugelmans, R.; Zhu, J. *Tetrahedron Lett.* **1997**, *38*, 5795-5798;
5 Boger, D. L.; Borzilleri, R. M.; Nukui, S.; Beresis, R. T. *J. Org. Chem.* **1997**, *62*, 4721-4736.
6 Evans, D. A.; Barrow, J. C.; Watson, P. S.; Ratz, A. M.; Dinsmore, C. J.; Evrard, D. A.; DeVries, K. M.; Ellman, J. A.; Rychnovsky, S. D.; Lacour, J. *J. Am. Chem. Soc.* **1997**, *119*, 3419-3420.
7 Nicolaou, K. C.; Boddy, C. N. C.; Natarajan, S.; Yue, T.-Y.; Li, H.; Bräse, S.; Ramanjulu, J. M. *J. Am. Chem. Soc.* **1997**, *119*, 3421-3422.
8 Rama Rao, A. V.; Reddy, K. L.; Rao, A. S.; Vittal, T. V. S. K.; Reddy, M. M.; Pathi, P. L. *Tetrahedron Lett.* **1996**, *37*, 3023-26
9 Janetka, J. W.; Rich, D. H. *J. Am. Chem. Soc.* **1997**, *119*, 6488-6495.
10 Pearson, A. J.; Zhang, P.; Bignan, G. *J. Org. Chem.* **1997**, *62*, 4536-4538.
11 Zhu, J.; Laib, T.; Chastanet, J. Beugelmans, R. *Angew. Chem. Int. Ed. Engl.* **1996**, *35*, 2517-2519.
12 Borchardt, A.; Still, W. C. *Synlett* **1995**, 539-540 and references cited therein.
13 Itokawa, H.; Takeya, K. *Heterocycles* **1993**, *35*, 1467-1501.
14 Boger, D. L.; Zhou, J.; Borzilleri, R. M.; Nukui, S.; Castle, S. L. *J. Org. Chem.* **1997**, *62*, 2054-2069 and references cited therein.
15 Bigot, A.; Beugelmans, R.; Zhu, J. *Tetrahedron* **1997**, *53*, 10753-10764.
16 Inaba, T.; Umezawa, I.; Yuasa, M.; Inoue, T.; Mihashi, S.; Itokawa, H.; Ogura, K. *J. Org. Chem.* **1987**, *52*, 2957-2958
17 Boger, D. L.; Yohannes, D. *J. Org. Chem.* **1991**, *56*, 1763-1767.
18 a) Jung, M. E.; Lazarova, T. I. *J. Org. Chem.* **1997**, *62*, 1553-1555; b) Boger, D. L.; Yohannes, D. *J. Org. Chem.* **1987**, *52*, 5283-5286. and references cited therein.
19 Beugelmans, R.; Singh, G. P.; Bois-Choussy, M.; Chastanet, J.; Zhu, J. *J. Org. Chem.* **1994**, *59*, 5535-5542.
20 Vergne, C.; Bois-Choussy, M.; Ouazzani, J.; Beugelmans, R.; Zhu, J. *Tetrahedron Asymmetry* **1997**, *8*, 391-398.
21 Wiberg, K. B. *Angew. Chem. Int. Ed. Engl.* **1986**, *25*, 312-322.
22 Benzylation of L-*N*-formyl-dopamine methyl ester gave equal amount of two possible mono benzylated compounds, see: Konda, M.; Takayuki, S.; Yamada, S.-I. *Chem. Pharm. Bull.* **1975**, *23*, 1063-76.
23 Reaction between L-*N*-Boc-dopamine methyl ester and 4-fluoro-3-nitrotoluene (K_2CO_3, DMSO) gave equal amount of two possible mono arylated compounds. Bigot, A. unpublished results.
24 Bois-Choussy, M.; Neuville, L.; Beugelmans, R. Zhu, J. *J. Org. Chem.* **1996**, *61*, 9309-9322.
25 Rhee, E. S.; Shine, H. J. *J. Am. Chem. Soc.* **1986**, *108*, 1000-1006.
26 AM1 calculations showed that the 14-membered (m,p)-cyclophane is thermodynamically more stable compound. Bigot, A. unpublished results.