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First approach to the cycloisodityrosine unit of RA-IV

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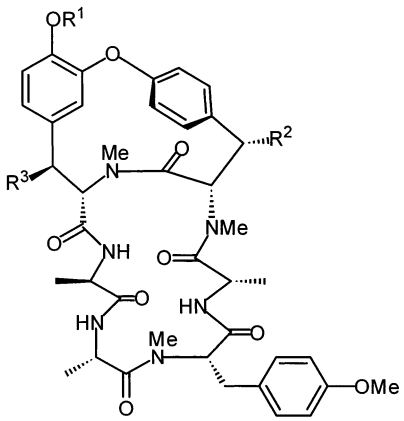
Abstract—The syntheses of the methyl (2*S*,3*S*)-2-amino-3-(3-hydroxy-4-methoxyphenyl)-3-*t*-butyldimethylsilyloxypropanoate and a precursor of the cycloisodityrosine unit of RA-IV are described.

Bouvardin **1**, a bicyclic hexapeptide isolated from *Bouvardia ternifolia*,[1] represents the initial member of a growing class of potent antitumor antibiotics. To date, 16 congeners (RA-I–RA-XVI) have been identified and their relative and absolute configurations have been determined.[2] These bicyclic compounds are characterized by an 18-membered peptide ring and a bridged 14-membered cycloisodityrosine unit that constitutes the pharmacophore.[3] This cycloisodityrosine unit is composed by two tyrosines for the majority of the compounds of this family. Three compounds include a β-hydroxytyrosine with *anti* stereochemistry in their cycloisodityrosine unit: Bouvardin **1**, RA-IV **2** and RA-VI **4**. Whereas the syntheses of RA-V **3** and RA-VII **5** are well documented,[4] only a total synthesis of Bouvardin and RA-VI was reported using Ullman macrocyclisation to obtain the cycloisodityrosine unit.[5] To our knowledge, the synthesis of the cycloisodityrosine unit of RA-IV has never been described.

A novel cycloetherification methodology based on intramolecular S_NAr reaction has been recently developed[6] and used for the synthesis of RA-VII **5**.[4e,f]

In connection with our continued work on α-amino β-hydroxy acids,[7] we report the synthesis of the *anti* β-hydroxytyrosine component of the 14-membered ring of RA-IV and the first preparation of a precursor of its cycloisodityrosine unit **6**.



1 Bouvardin $R^1 = R^2 = H$; $R^3 = OH$
2 RA-IV $R^1 = Me$; $R^2 = H$; $R^3 = OH$
3 RA-V $R^1 = R^2 = R^3 = H$
4 RA-VI $R^1 = Me$; $R^2 = OH$; $R^3 = H$
5 RA-VII $R^1 = Me$; $R^2 = R^3 = H$

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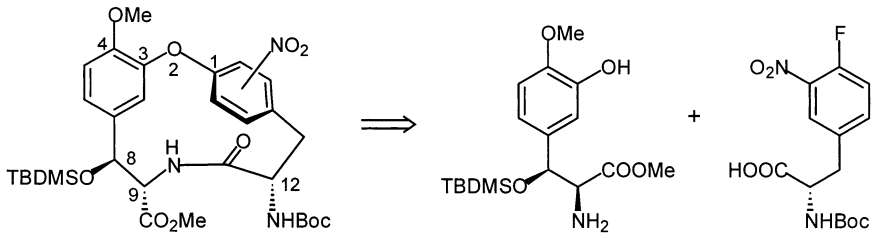
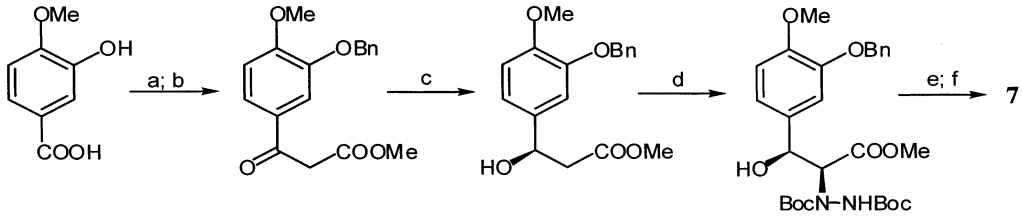


6 7 8



9 10 11 12

(a) NaH, $PhCH_2Br$, DMF ; NaOH, 2N, MeOH (60%). (b) $SOCl_2$; $KO_2CCH_2CO_2Me$, $MgCl_2$, Et_3N, CH_3CN (85%). (c) H_2, 10 bar, 1% (S)-Binap Ru Br_2, CH_2Cl_2, room temperature, 78h (83%, ee=90%). (d) MeZnBr, LDA, DBAD, -78°C then aq. NH_4Cl (50%, de>95%). (e) TBDMSOTf, 2,6-lutidine ; H_2, Pd/C 10%, MeOH (96%). (f) CF_3CO_2H, CH_2Cl_2 ; H_2, Raney Ni, ultrasounds, MeOH (50%).

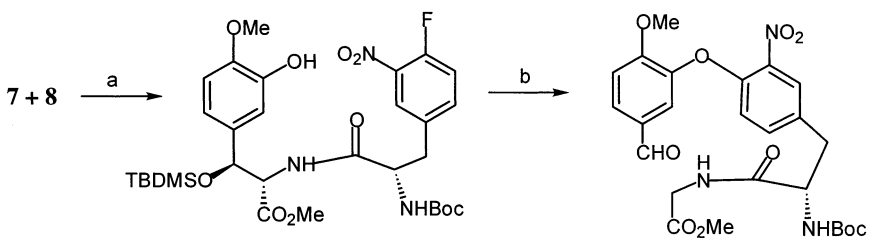
6 could be obtained by a peptide coupling reaction between the protected β-hydroxytyrosine **7** and the *N*-Boc protected (*S*)-4-fluoro-3-nitrophenylalanine **8**[8] followed by an S_NAr macrocyclisation. The key steps to obtain **7** are the asymmetric hydrogenation of a β-ketoester[9] and the diastereoselective electrophilic amination of the resulting β-hydroxyester.[7]

The synthesis started from the commercially available 3-hydroxy-4-methoxybenzoic acid **9** which was homologated to the β-ketoester **10**[10] after protection of the phenolic functionality as a benzyl ether. **10** was hydrogenated enantioselectively at room temperature and low pressure in the presence of 1% of (*S*)-Binap $RuBr_2$. The (*R*)-β-hydroxyester **11** was obtained in 83% yield and 90% ee.[11] The zinc enolate of **11** was then aminated with *t*-butylazodicarboxylate: the electrophilic amination was highly diastereoselective, providing the *anti* α-hydrazino-β-hydroxyester **12** as the only detectable diastereomer.[12] To achieve the synthesis of **7**, the alcohol was protected as a *t*-butyldimethylsilylether and the benzyl ether hydrogenolyzed quantitatively. After deprotection of the *t*-butyl carbamates, the N–N bond of the hydrazine was cleaved with H_2 in the presence of Raney Ni under ultrasounds. (2*S*,3*S*)-**7** was purified by silica gel flash chromatography and isolated in 50% yield and 90% enantiomeric excess.[13]

The peptide coupling reaction of **7** with optically pure (*S*)-**8** was performed under classical conditions. The major diastereomer of the dipeptide **13** was obtained in 80% yield after silica gel flash chromatography.

A first attempt at the intramolecular S_NAr reaction was run in the presence of K_2CO_3 and 3 Å molecular sieves in DMSO at room temperature for 1 h. The cycloetherification occured under these conditions with a retro-Aldol reaction giving **14**. During the S_NAr reaction, fluoride ions are liberated leading to *t*-butyldimethylsilyl ether deprotection and subsequent retro-Aldol cleavage.

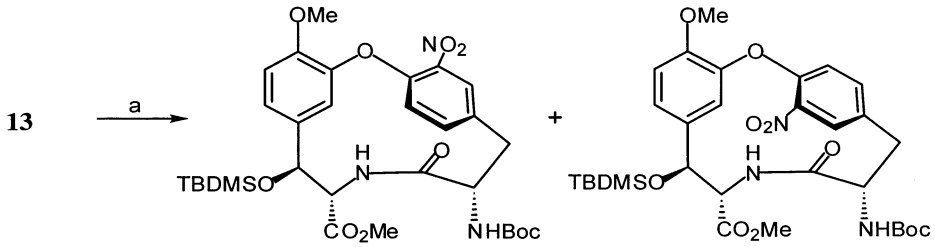
A similar observation was reported by Boger et al. for the synthesis of the 16-membered D–E ring system of vancomycin. A successful macrocyclisation was



13 14

(a) EDCI, HOBt, CH_2Cl_2, room temperature, 1h (80%). (b) K_2CO_3 (4 equiv.), 3Å molecular sieves, DMSO (0.01M), room temperature, 1h (45%).

described using a mixture of K_2CO_3–$CaCO_3$: $CaCO_3$ being as an efficient scavenger of the liberated fluoride anion.[14]



6

(a) K_2CO_3-$CaCO_3$ (4 equiv./5 equiv.), 3Å molecular sieves, DMSO (0.01M), room temperature, 1h (10%).

These conditions were applied to the synthesis of the 14-membered ring of RA-IV. Treatment of a 0.01 M solution of the dipeptide **13** with K_2CO_3–$CaCO_3$ (4 equiv./5 equiv.) in the presence of 3 Å molecular sieves in DMSO for 1 h at room temperature afforded the desired macrocyle **6**.[15] After preparative thin layer chromatography, (8*S*,9*S*,12*S*)-**6** was isolated in 10% yield as an inseparable mixture of atropoisomers.

In conclusion, an efficient synthesis of the dipeptide unit **13** has been developed. In spite of the low macrocyclisation yield, this synthesis represents the first approach via an intramolecular S_NAr to a 14-membered ring system including a β-hydroxytyrosine **6**, which is the direct precursor of the cycloisodityrosine unit of RA-IV.

Acknowledgements

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8. We thank Dr. J. Zhu for the gift of *N*-Boc (*S*)-4-fluoro-3-nitrophenylalanine. For synthesis, see: Vergne, C.; Bois-Choussy, M.; Ouazzani, J.; Beugelmans, R.; Zhu, J. *Tetrahedron: Asymmetry* **1997**, *8*, 391–398 and references cited therein.
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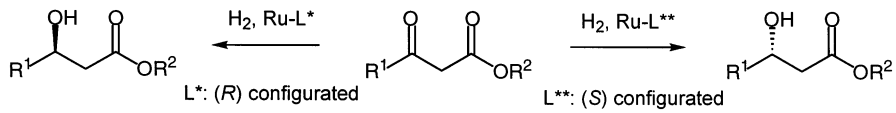
10. For the obtention of β-ketoesters, see: Clay, R. J.; Collom, T. A.; Karriek, G. L.; Wemple, J. *Synthesis* **1993**, 290–292.
11. The asymmetric hydrogenation of β-ketoesters in the presence of the Ru(II) catalyst bearing atropoisomeric ligands proceeds in a predictable sense, as shown below:



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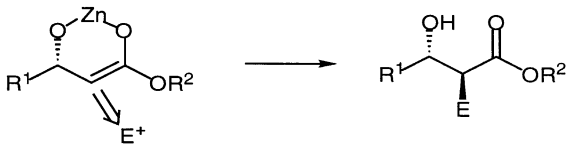
(*R*)-**11**: ^{1}H NMR (200 MHz, $CDCl_3$), δ (ppm): 7.40 (m, 5H); 6.90 (m, 3H); 5.15 (s, 2H); 5.04 (dd, J=8.5; 4.5 Hz, 1H); 3.88 (s, 3H); 3.71 (s, 3H); 2.73 (dd, J=16.3; 8.5 Hz, 1H); 2.63 (dd, J=16.3; 4.5 Hz, 1H). e.e.=90% measured by ^{1}H NMR in the presence of 0.1 equiv. of (+)-[Eu(Tcf)$_3$].

$[\alpha]_D^{20}=+24$ (c 1.1, $CHCl_3$). Anal. calcd for $C_{18}H_{20}O_5$: C, 68.34; H, 6.37. Found: C, 68.37; H, 6.44.

12. The *anti* diastereoselectivity of the electrophilic amination was explained as earlier described via the chelated zinc enolate:



See: Greck, C.; Bischoff, L.; Ferreira, F.; Pinel, C.; Piveteau, E.; Genêt, J. P. *Synlett* **1993**, 475–477. Ferreira, F.; Greck, C.; Genêt, J. P. *Bull. Soc. Chim. Fr.* **1997**, *134*, 615–621. Poupardin, O.; Greck, C.; Genêt, J. P. *Synlett* **1998**, 1279–1281.

(2*S*,3*S*)–**12**: ^1H NMR (200 MHz, $CDCl_3$), δ (ppm): 7.32 (m, 5H); 6.95 (m, 3H); 5.20 (m, 1H); 5.13 (s, 2H); 4.80 (m, 1H); 3.87 (s, 3H); 3.70 (sl, 3H); 1.44 (s, 9H); 1.41 (s, 9H). e.e. = 90%. $[\alpha]_D^{20}=-44$ (c 1, EtOH). Anal. calcd for $C_{28}H_{38}N_2O_9$: C, 61.52; H, 7.00; N, 5.12. Found: C, 61.50; H, 6.99; N, 5.06.

13. (2*S*,3*S*)-**7**: ^1H NMR (200 MHz, $CDCl_3$), δ (ppm): 6.8 (m, 3H); 4.71 (d, $J=6.6$ Hz, 1H); 3.88 (s, 3H); 3.71 (s, 3H); 3.62 (d, $J=6.6$ Hz, 1H); 0.86 (s, 9H); 0.02 (s, 3H); –0.16 (s, 3H). e.e. = 90%. $[\alpha]_D^{20}=+59$ (c 0.6, $CHCl_3$). Anal. calcd for $C_{17}H_{29}NO_5Si$: C, 57.44; H, 8.22; N, 3.94. Found: C, 57.42; H, 8.19; N, 4.00.

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15. **6**: ^1H NMR (400 MHz, $CDCl_3$), δ (ppm): 7.82 (s, 1H); 7.5 (m, 1H); 7.45 (m, 1H); 6.76 (d, $J=8.2$ Hz, 1H); 6.62 (d, $J=8.2$ Hz, 1H); 5.76 (m, 1H); 5.52 (m, 1H); 5.32 (m, 1H); 4.83 (d, $J=6.2$ Hz, 1H); 4.3 (d, $J=6.2$ Hz, 1H); 4.11 (m, 1H); 4 (s, 3H); 3.65 (m, 1H); 3.45 (dd, $J=13$ and 4 Hz, 1H); 3.29 (s, 3H); 1.46 (s, 9H); 0.8 (s, 9H); 0.05 (s, 3H); –0.13 (s, 3H). MS m/z (CI) 646 (M^++1).