Pergamon

Tetrahedron: *Asymmetry* 10 (1999) 99–105

TETRAHEDRON: *ASYMMETRY*

A synthetic approach to diaryl ethers using the Robinson annulation

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Received 20 October 1998; accepted 9 November 1998

Abstract

An alternative synthetic approach to diaryl ethers has been developed. In the key transformation, Robinson annulation of nonracemic aldehydes **16a**,**b**, derived from L-glutamic acid 5-methyl ester and phenoxymethylvinyl ketone, provided α-phenoxyenones **17a**,**b**. The Cbz-protected oxazolidine **17b** was further converted into the diaryl ether **18b** utilizing an oxidative selenation protocol. © 1999 Elsevier Science Ltd. All rights reserved.

1. Introduction

The diaryl ether functionality is a key structural subunit in numerous bioactive natural products.[1] The simplest member, isodityrosine,[2] is formed in the cyclic tripeptide K-13[3] as the result of oxidative phenolic coupling of two tyrosine residues. More elaborate examples include cycloisodityrosines **1**–**3**[4] (Scheme 1), the bicyclic hexapeptide bouvardin **4**–**6**,[4] and highly complex glycopeptide antibiotics such as the vancomycin family.[5] In all cases the diaryl ether linkages are presented within macrocyclophane frameworks having a ring size of either 14,[4] 16,[5] or 17[3] members. Many important achievements have resulted in the total syntheses of all but the most complicated diaryl ether containing natural products.[1] From a synthetic standpoint one of the greater challenges remaining in this area is concerned with the 14-membered ring systems[4] that are present in **4**–**6** and the G-O-F subunit of teicoplanin.[6] At present, the only viable approach to cycloisodityrosines incorporates an intramolecular S_NAr based cyclo-etherification reaction, first developed by Zhu and co-workers.[1c] Initial studies encountered difficulties with facile epimerization at the C-9 stereocenter of the 14-membered network which is believed to be related to the location of the aromatic nitro substituent derived from a 3-fluoro-4-nitrophenylalanine coupling partner.[4i,k] However, further study revealed that by reversing the direction of coupling, i.e., incorporating 4-fluoro-3-nitrophenylalanine as the electrophilic partner with the appropriate dopa deri-

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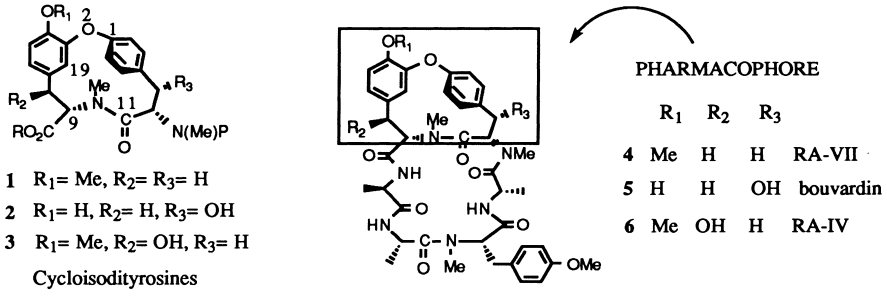
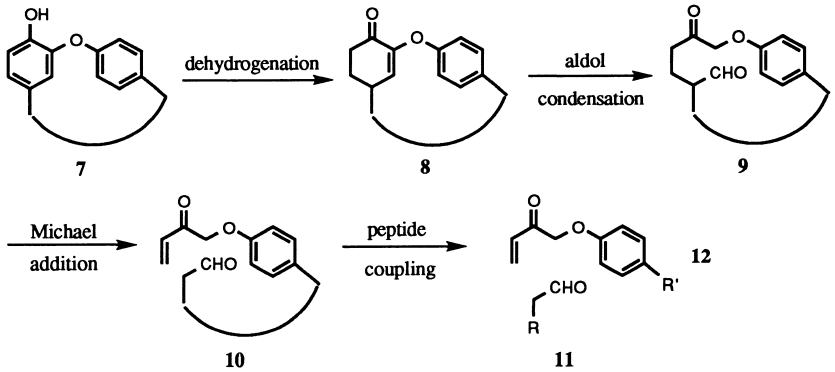
PII: S0957-4166(98)00466-2

vative, this difficulty can be avoided.[41] Efficient chemical routes to the hydroxylated cycloisodityrosines **2** and **3** still remain a desirable objective.



Scheme 1.

Much effort has been devoted towards the development of strategies to construct the key diaryl ether linkage[7] and can be grouped into five distinct approaches.[1b] However, one of the challenges that remains includes an efficient method for the construction of the strained 14-membered ring hydroxylated isodityrosine subunit present in bouvardin[4] and RA-IV.[1] Our interest in this area is to develop an alternative approach to the strained 14-membered ring diaryl ethers **7** based on a Robinson annulation[8] that can be conducted under mild, weakly basic reaction conditions (Scheme 2). In this way sensitive β-elimination and epimerization problems can hopefully be avoided. Application of a dehydrogenation transform to **7** would lead to enone **8**, which can be seen to arise via an aldol condensation[8,9] process from the 16-membered ring precursor **9** by a macrocyclic two-atom ring contraction.[9] Macrocycle **9** should be easily obtained from acyclic precursors **10**–**12** through Michael addition and peptide coupling reactions.

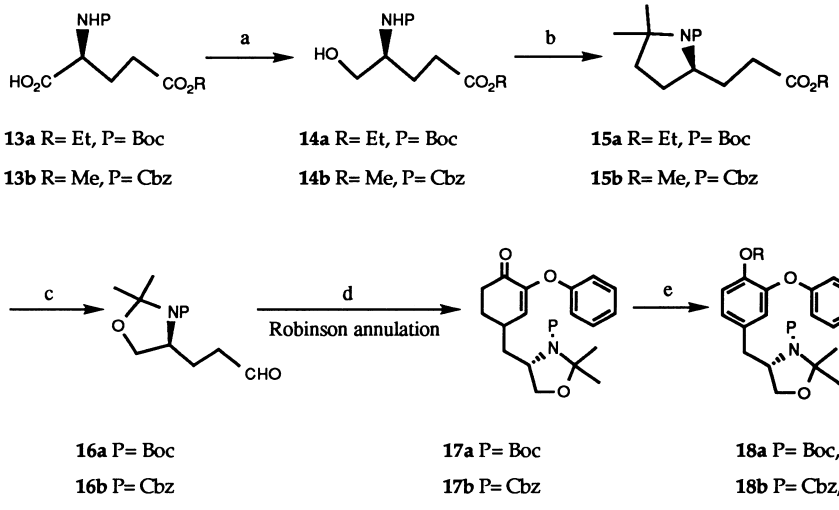


Scheme 2.

2. Results and discussion

Based on the above retrosynthetic analysis, a Robinson annulation[8,10] approach to diaryl ethers has been demonstrated in our laboratory as revealed below (Scheme 3). Starting from the commercially available L-glutamic 5-ethyl ester, the Boc protected amino alcohol **14a** is processed from **13a** in more than 84% overall yield utilizing reported methodology.[11] In a straightforward manner, the Cbz-protected amino alcohol **14b** was also made in high overall yield from L-glutamic acid 5-methyl ester **13b**. Refluxing **14a**–**b** with DMP and TsOH in benzene provides oxazolidines **15a**–**b** in 78–86% yields. Controlled DIBAL-H reduction delivers aldehydes **16a**–**b** in 87–90% yield. Robinson annulation[8,10] with phenoxymethyl vinyl ketone[12] provides α,β-unsaturated ketones **17a**–**b** in 47–58% yields. It should be pointed out that this Robinson annulation is a one-pot reaction involving three steps: (i) reflux of the

aldehydes with 1.0–1.5 equiv. of morpholine in benzene using molecular sieves for removal of water; (ii) Michael addition of phenoxymethyl vinyl ketone to the newly generated enamine at 0°C; (iii) aldol condensation of the resulting Michael product in the boiling benzene solution. Further transformation of the Robinson annulation product into the diaryl ether was explored using several approaches from the literature.[13] For example, reaction of **17a** with TipsOTf followed by DDQ oxidation of the intermediate silylenol ether afforded the final diaryl ether **18a** in a very poor yield (less than 10%). The $CuBr_2/LiBr$[13a] and $Mn(OAc)_3$[13c] oxidation reactions of the Robinson adducts have also been proven impractical. Finally, treatment of **17b** with PhSeCl[2c,13d] or PhSeCl/LHMDS followed by H_2O_2 oxidation, without isolation of the intermediate selenium product, gave the desired diaryl ether **18b** in 41–60% yield.



Key: (a) (i) N-hydroxysuccinimide (HOSu), DCC, EtOAc; (ii) $NaBH_4$, THF/EtOH or MeOH, 0 °C; (b) DMP, benzene, reflux, 3h, 78-86%; (c) DIBAL-H, PhMe, -78 °C, 86-90%; (d) $PhOCH_2COCH{=}CH_2$, Robinson reaction; (e) For **17a→18a:** (i) TipsOTf, Et_3N, 0 to 25 °C; (ii) DDQ, PhH, reflux; For **17b→18b:** (i) PhSeCl, EtOAc, reflux; (ii) H_2O_2.

Scheme 3.

In summary, this simple model study has established an alternative methodology for construction of diaryl ether bonds based on a Robinson aromatization protocol. Continued efforts will evaluate the viability of this approach as an alternative to the classical Ullmann reaction and the S_NAr approaches for synthesis of 14-membered cycloisodityrosines.

3. Experimental section

All reagents were of commercial quality (Aldrich, Fluka, Sigma) and were used as received. Solvents were dried and purified using standard techniques. Infrared spectra of samples were obtained on a Perkin–Elmer 1600 Series FTIR. ^1H NMR spectra were recorded at 400 MHz (Varian 400 NMR). ^{13}C NMR were measured at 100.59 MHz using $CDCl_3$ as solvent. HRMS was provided by the Mass Spectrometry Laboratory, Department of Chemistry and Biochemistry, Montana State University, Bozeman, MT 59717.

3.1. N-*Boc*-L-*Glutamic acid γ-ethyl ester* ***13a***

To a stirred solution of L-glutamic acid γ-ethyl ester (8.75 g, 50 mmol) in 150 ml of water was added $NaHCO_3$ (9.2 g, 110 mmol) at 0°C, followed by $(Boc)_2O$ (11.5 g, 53 mmol) in 150 ml dioxane for 2–3 h. The reaction mixture was stirred at rt overnight. The solution was extracted with ethyl ether (3×100 ml). The aqueous layer was acidified to pH 2 with 10% HCl. The product was extracted by ethyl acetate (2×100 ml). The organic layer was washed with brine and dried over $MgSO_4$. The solution was passed through a short pad of silica gel (EtOAc) and concentrated to provide **13a** (14.0 g, 100%) as semi-solid. $[\alpha]_D^{25}$ +2.4 (c 1.0, EtOAc); IR (film) 3340–3000, 2980, 1730–1650, 1450, 1390, 1250, 1160, 1050 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 5.40 (d, 1H), 4.61 (m, 1H), 4.12 (q, J=8.0 Hz, 2H), 2.45 (m, 2H), 2.20 (m, 1H), 2.00 (m, 1H), 1.43 (s, 9H), 1.24 (t, J=8.0 Hz, 3H); ^{13}C NMR (100.59 MHz, $CDCl_3$) δ 176.11 (d), 173.08, 155.66, 80.34, 67.02, 60.80, 52.84 (d), 30.42 (d), 28.26, 14.12.

3.2. N-*Cbz*-L-*Glutamic acid γ-methyl ester* ***13b***

To a stirred solution of L-glutamic acid γ-methyl ester (16.1 g, 100 mmol) in 220 ml of water and 100 ml of dioxane was added Na_2CO_3 (10.6 g, 100 mmol) at 0°C, followed by benzyl chloroformate (17.2 g, 101 mmol) in 120 ml dioxane for 2–3 h. The reaction mixture was stirred at rt overnight. The solution was extracted with ethyl acetate (3×100 ml). The aqueous layer was acidified to pH 2 with 6 N HCl. The product was extracted with ethyl acetate (2×100 ml). The organic layer was washed with brine and dried over $MgSO_4$. The solution was passed through a short pad of silica gel (EtOAc) and concentrated to provide 26.9 g (91%) of **13b** as semi-solid. $[\alpha]_D^{25}$ +0.5 (c 0.93, EtOAc); IR (film) 3330–3000, 2950, 1730–1690, 1540, 1450, 1340, 1220, 1050 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.33 (m, 5H), 5.49 (d, J=7.2 Hz), 5.11 (s, 2H), 4.43 (m, 1H), 3.66 (s, 3H), 2.47 (m, 2H), 2.24 (m, 1H), 2.04 (m, 1H); ^{13}C NMR (100.59 MHz, $CDCl_3$) δ 176.02, 173.50, 156.17, 135.94, 128.53, 128.22, 128.10, 67.22 (d), 53.18 (d), 51.90, 29.99 (d), 27.23.

3.3. *Ethyl (4*S*)*-N-*(*t-*butoxycarbonyl)amino-5-hydroxypentanoate* ***14a***

To a stirred solution of *N*-Boc-L-glutamic acid γ-ethyl ester (14.0 g, 50 mmol) in 250 ml of ethyl acetate was added *N*-HOSu (6.9 g, 60 mmol) and DCC (12.4 g, 60 mmol) at 0°C. The mixture was allowed to warm to rt overnight. The mixture was filtered and the solution was washed with satd $NaHCO_3$ and brine, dried over $MgSO_4$, and concentrated to provide 19 g of crude product. To a stirred solution of the crude product in 150 ml THF was added 2.0 g of $NaBH_4$ at 0°C, followed by 50 ml of EtOH over 30 min. The reaction mixture was stirred for an additional 15 min and then quenched with satd NH_4Cl. The product mixture was extracted with ethyl acetate and the separated organic phase was washed with brine, dried over $MgSO_4$ and concentrated in vacuo. The oily product was purified by flash chromatography on silica gel with 65 to 70% EtOAc:hexanes to provide **14a** (11.2 g, 85%) as a colorless oil. $[\alpha]_D^{25}$ −16 (c 1.3, EtOAc); IR (film) 3620–3390, 2980, 1730–1680, 1385, 1170, 1050 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 4.90 (br d, 1H), 4.11 (q, J=7.2 Hz, 2H), 3.58 (br s, 2H), 3.53 (br s, 1H), 2.92 (br s, 1H), 2.37 (m, 2 H), 1.86 (m, 1H), 1.74 (m, 1H), 1.40 (s, 9H), 1.22 (t, J=7.2 Hz, 3H); ^{13}C NMR (100.59 MHz, $CDCl_3$) δ 173.78, 156.18, 79.52, 65.01, 60.58, 52.24, 30.87, 28.29, 26.23, 14.12.

3.4. *Methyl (4*S*)*-N-*(Benzyloxycarbonyl)amino-5-hydroxypentanoate* ***14b***

To a stirred solution of *N*-Cbz-L-glutamic acid γ-methyl ester (7.0 g, 24 mmol) in 100 ml of ethyl acetate was added *N*-HOSu (2.9 g, 25 mmol) and DCC (5.2 g, 25 mmol) at 0°C. The mixture was

allowed to warm to rt overnight. The mixture was filtered and the resulting solution was washed with satd $NaHCO_3$ and brine, dried over $MgSO_4$, and concentrated to provide 9.5 g of crude product. To a stirred solution of the crude product in 75 ml of THF was added 1.0 g of $NaBH_4$ at 0°C followed by 25 ml of MeOH over 30 min. The reaction mixture was stirred for an additional 15 min and quenched with satd NH_4Cl. The product was extracted with ethyl acetate. The organic phase was washed with brine, dried over $MgSO_4$ and concentrated in vacuo. The oily product was purified by flash chromatography on silica gel with 65 to 70% EtOAc:hexanes to provide **14b** (5.8 g, 87%) as a colorless oil. $[\alpha]_D^{25}$ −21 (c 0.91, EtOAc); IR (film) 3350–3060, 3030, 2950, 1730–1680, 1540, 1450, 1370, 1250, 1170, 1060 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.35 (m, 5H), 5.08 (s, 2H), 5.05 (br s, 1H), 3.72 (m, 2H), 3.65 (s, 3H), 3.60 (br d, 1H), 2.42 (m, 2H), 2.27 (br s, 1H), 1.87 (m, 1H), 1.83 (m, 1H); ^{13}C NMR (100.59 MHz, $CDCl_3$) δ 174.23, 156.57, 136.30, 128.53 (d), 128.16, 128.07, 66.83, 64.77, 52.72, 51.84, 30.54, 26.08.

*3.5. (4S)-3-(t-Butoxycarbonyl)-2,2-dimethyl-4-(ethoxycarbonylethyl)oxazolidine **15a***

To a solution of **14a** (6.0 g, 23 mmol) in 240 ml of benzene was added 18 ml of DMP and 180 mg of TsOH. The reaction mixture was refluxed for 0.5 h and slowly distilled over 3 h until 120 ml of benzene was removed. The mixture was quenched with 0.3 ml of pyridine and concentrated in vacuo. The residue was subjected to flash column chromatography using 15% EtOAc:hexanes to provide **15a** (6.0 g, 86%) as a colorless oil. $[\alpha]_D^{25}$ +22 (c 0.95, EtOAc); IR (film) 2980, 1730, 1690, 1460, 1385, 1260, 1180, 1070 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 4.12 (q, J=8.8 Hz, 2H), 3.94–3.71 (m, 2H+1H), 2.32 (m, 2H), 2.03–1.89 (m, 2H), 1.59–1.43 (m, 6H), 1.46 (s, 9H), 1.25 (t, 3H); ^{13}C NMR (100.59 MHz, $CDCl_3$) δ 173.02, 159.29 (d), 93.87 (d), 80.06 (d), 66.92 (d), 60.40, 56.72 (d), 31.02 (d), 28.87, 28.38, 27.50 (d), 24.38 (d), 14.15.

*3.6. (4S)-3-(Benzyloxycarbonyl)-2,2-dimethyl-4-(methoxycarbonylethyl)oxazolidine **15b***

To a solution of **14b** (5.0 g, 18 mmol) in 100 ml of dried acetone was added 24 ml of DMP and 500 mg of TSOH. The reaction mixture was stirred at rt overnight, quenched with 0.5 ml of pyridine, and then concentrated in vacuo. The residue was dissolved in 100 ml of EtOAc and 20 ml of satd $NaHCO_3$. The organic phase was washed with satd $NaHCO_3$ and brine, and dried over $MgSO_4$. After concentration, the residue was subjected to flash column chromatography using 15% EtOAc:hexanes to provide **15b** (4.8 g, 84%) as an oil. $[\alpha]_D^{25}$ +6.4 (c 1.2, EtOAc); IR (film) 2950, 1760, 1670, 1580, 1490, 1350, 1250, 1070 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.34 (m, 5H), 5.16 (q, J=12 Hz), 4.05–3.95 (m, 2H), 3.78–3.76 (d, 1H), 3.68–3.60 (d, 3H), 2.40–2.31 (m, 2H), 2.10–1.80 (m, 2H), 1.64–1.45 (q, 6H); ^{13}C NMR (100.59 MHz, $CDCl_3$) δ 173.05, 152.17 (d), 136.16, 128.38, 127.86, 127.77, 94.15 (d), 67.01 (d), 66.44, 56.09 (d), 51.45, 30.39 (d), 28.69 (d), 26.41 (d), 22.83 (d).

*3.7. (4S)-3-(t-Butoxycarbonyl)-2,2-dimethyl-4-(3-oxo-propyl)oxazolidine **16a***

To a stirred solution of **15a** (4.8 g, 16 mmol) in 40 ml of toluene was added 16 ml of DIBAL-H (1.5 M in toluene), dropwise at −78°C. The reaction was kept at −78°C for 45 min, and then quenched with 1 ml of methanol. The reaction mixture was diluted with 25 ml of 1 N HCl at 0°C, and then stirred for 15 min. The solution was extracted with 2×50 ml of EtOAc. The combined organic layer was washed with brine and dried over $MgSO_4$. The residue was purified by flash column chromatography over silica gel using 20% EtOAc:hexanes to provide **16a** (3.8 g, 90%) as a colorless oil. The aldehyde was then immediately

subjected to the next reaction. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.75 (s, 1H), 3.82–3.97 (m, 2H), 3.74 (d, 1H), 2.47 (m, 2H), 1.90–2.02 (m, 2H), 1.58–1.40 (m, 6H), 1.46 (s, 9H).

*3.8. (4S)-3-(Benzyloxycarbonyl)-2,2-dimethyl-4-(3-oxo-propyl)oxazolidine **16b***

To a stirred solution of **15b** (6.9 g, 21 mmol) in 70 ml of toluene was added 20 ml of DIBAL-H (1.5 M in toluene), dropwise at −78°C. The reaction was kept at −78°C for 45 min, quenched with 1 ml of methanol, and then diluted with 200 ml of ethyl acetate. The organic layer was washed in 2×15 ml of 6 N HCl and 2×15 ml of brine, then dried over $MgSO_4$. The residue was purified by flash column chromatography over silica gel using 20% EtOAc:hexanes to provide **16b** (5.2 g, 87%) as a colorless oil. The aldehyde was then immediately subjected to the next reaction. ^{1}H NMR (400 MHz, $CDCl_3$, chemical shifts sensitive to the ratio of rotamers) δ 9.78–9.68 (d, 1H), 7.35 (m, 5H), 5.10 (m, 2H), 4.02–3.96 (m, 2H), 3.71 (d, 1H), 2.50–2.38 (m, 2H), 1.96 (m, 2H), 1.62–1.42 (q, 4H).

*3.9. The α,β-unsaturated Robinson adduct **17a***

The adduct **17a** was synthesized in the same manner as the adduct **17b**. Yield: 48%. The α,β-unsaturated Robinson adduct was then immediately subjected to the next reaction. ^{1}H NMR (400 MHz, $CDCl_3$, chemical shifts sensitive to ratios of both rotamers and diastereomers) δ 7.28 (m, 5H), 6.92–7.05 (m, 5H), 6.21–6.00 (m, H), 4.03–3.81 (m, 2H), 3.66 (d, 1H), 2.65 (m, 1H), 2.52 (m, 2H), 2.17 (m, 1H), 1.88–1.61 (m, 3H), 1.58–1.37 (m, 6H), 1.42 (s, 9H).

*3.10. The α,β-unsaturated Robinson adduct **17b***

A solution of **16b** (4.8 g, 16.5 mmol) in 70 ml of benzene was added to 1.43 ml (16 mmol) of morpholine. The reaction mixture was refluxed for 3 h using 4 Å power molecular sieves in a Soxhlet apparatus for the removal of water. The mixture was concentrated to about 30 ml, and then a solution of phenoxymethyl vinyl ketone (3.3 g, 20 mmol) in 30 ml of benzene was added at 0°C. The reaction was slowly warmed up to rt overnight and then heated at reflux for 3 h. After removal of benzene, the residue was dissolved in 30 ml of H_2O and 30 ml of MeOH. The resulting mixture was refluxed for 8 h. The solution volume was reduced in vacuo to approximately one-half of the original and then extracted with ethyl acetate. The organic layer was washed with brine, dried over $MgSO_4$, and concentrated in vacuo. The residue was purified by flash column chromatography over silica gel using 20–30% EtOAc:hexanes to provide **17b** (4.1 g, 58%) as a colorless oil. The adduct was immediately subjected to the next reaction. ^{1}H NMR (400 MHz, $CDCl_3$, chemical shifts sensitive to ratios of both rotamers and diastereomers) δ 7.32 (m, 5H), 7.05–6.82 (m, 5H), 6.18–5.92 (m, 1H), 5.16–4.97 (m, 2H), 4.09–4.82 (m, 2H), 3.72 (d, 1H), 2.85–2.05 (m, 3H), 1.98–1.75 (m, 2H), 1.62–1.41 (m, 6H+2H).

3.11. N-*Benzyloxycarbonyl*-N,O-*isopropylidenyl-3-phenoxy-(S)-tyrosinol **18b***

To a solution of **17b** (0.30 g, 0.69 mmol) in 6 ml of EtOAc was added PhSeCl (0.29 g, 1.5 mmol) and K_2CO_3 (0.10 g, 0.75 mmol). The mixture was heated at reflux for 1–3 h (monitored by TLC). After cooling to rt, the mixture was diluted with EtOAc and then washed with water and brine. The organic layer was dried over $MgSO_4$ and concentrated in vacuo. The residue was dissolved in a solution of 0.5 ml of pyridine in CH_2Cl_2 (6 ml). After cooling to 0°C, 0.5 ml of H_2O_2 was added slowly. The mixture was warmed up to rt for 1 h and extracted with ethyl acetate. The residue was chromatographed over

silica gel using 20% EtOAc:hexanes to provide **18b** (0.15 g, 41%) as a white foam. $[\alpha]_D^{25}$ −17 (c 0.98, EtOAc); IR (film) 3060, 2980, 2850, 1690, 1595, 1500, 1460, 1385, 1250, 1170, 1060 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$, chemical shifts sensitive to the ratio of rotamers) δ 6.61–7.39 (series of m, 13H), 5.51 (br s, 1H), 5.02–5.19 (two A_2B_2 q, 2H, Cbz benzylic), 4.03 and 3.95 (two sets of m, 1H, αH), 3.70–3.80 (m, 2H), 2.90 and 3.10 (two sets of dd, 1H, dopa benzylic), 2.55 (t, 1H, dopa benzylic), 1.42, 1.48, 1.50 and 1.58 (series of s, 6H, oxazolidine Me); ^{13}C NMR (100.59 MHz, $CDCl_3$) δ major isomer 156.70, 152.20, 146.20, 143.15, 136.25, 130.68, 129.92, 128.53, 128.13, 127.98, 125.49, 123.61, 119.72, 117.76, 116.21, 94.80, 66.74, 66.23, 59.00, 38.85, 26.62, 23.14; minor isomer 152.60, 127.10, 125.85, 120.00, 116.10, 67.08, 65.77, 59.58, 37.55, 27.50, 24.56; HRMS m/e 433.1883 ($C_{26}H_{27}NO_5$ requires 433.1889).

Acknowledgements

This research was supported by funds provided from the Montana NSF EPSCoR Program (MONTS) and the Research Office, University of Montana.

References

1. For recent reviews of synthetic efforts towards diaryl ether peptides, see: (a) Williams, R. M.; Hendrix, J. A. *Chem. Rev*. **1992**, *92*, 889–917. (b) Rao, A. V.; Gurjar, M. K.; Reddy, K. L.; Rao, A. S. *Chem. Rev*. **1995**, *92*, 2135–2167. (c) Zhu, J. *Synlett* **1997**, 133–144.
2. (a) Boger, D. L.; Yohannes, D. *Tetrahedron Lett*. **1989**, *30*, 2053–2056. (b) Jung, M. E.; Jachiet, D.; Rohloff, J. C. *Tetrahedron Lett*. **1989**, *30*, 4211–4214. (c) Jung, M. E.; Starkey, L. S. *Tetrahedron* **1997**, *53*, 8815–8824.
3. (a) Evans, D. A.; Ellman, J. A. *J. Am. Chem. Soc*. **1989**, *111*, 1063–1072. (b) Boger, D. L.; Yohannes, D. *J. Org. Chem*. **1990**, *55*, 6000–6017.
4. For the synthesis of deoxybouvardin and the pharmacophores of RA I–VII, see: (a) Boger, D. L.; Yohannes, D. *J. Am. Chem. Soc*. **1991**, *113*, 1427–1429. (b) Boger, D. L.; Myers Jr., J. B. *J. Org. Chem*. **1991**, *56*, 5385–5390. (c) Boger, D. L.; Yohannes, D.; Myers Jr., J. B. *J. Org. Chem*. **1992**, *57*, 1319–1321. (d) Boger, D. L.; Yohannes, D. *J. Org. Chem*. **1988**, *53*, 487–549. (e) Inaba, T.; Umezawa, I.; Yuasa, M.; Inoue, T.; Mihashi, S.; Itokawa, H.; Ogura K. *J. Org. Chem*. **1987**, *52*, 2957–2958. (f) Boger, D. L.; Patane, M. A.; Zhou, J. *J. Am. Chem. Soc*. **1994**, *116*, 8544–8556. (g) Inoue, T.; Sasaki, T.; Takayanagi, H.; Harigaya, Y.; Hoshino, O.; Hara, H.; Inaba, T. *J. Org. Chem*. **1996**, *61*, 3936–3937. (h) Boger, D. L.; Zhou, J. *J. Org. Chem*. **1996**, *61*, 3938–3939. (i) Boger, D. L.; Zhou, J.; Borzilleri; Nukui, S.; Castle, S. L. *J. Org. Chem*. **1997**, *62*, 2054–2069. (j) Beugelmans, R.; Bigot, A.; Bois-Choussy, M.; Zhu, J. *J. Org. Chem*. **1996**, *61*, 771–774. (k) Bigot, A; Beugelmans, R.; Zhu, J. *Tetrahedron* **1997**, *53*, 10753–10764. (l) Bigot, A.; Zhu, J. *Tetrahedron Lett*. **1998**, *39*, 551–554. (m) For structures and antitumor activities of RA derivatives (bouvardin), see: Itokawa, H.; Kondo, K.; Hitotsuyanagi, Y.; Nakamura, A.; Morita, H.; Takeya, K. *Chem. Pharm. Bull*. **1993**, *41*, 1266–1269.
5. 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.
6. Beugejmans, R.; Bourdet, S.; Zhu, J. *Tetrahedron Lett*. **1995**, *36*, 1279–1282.
7. Feng, X.; Olsen, R. K. *J. Org. Chem*. **1992**, *57*, 5811–5812.
8. (a) Gawley, R. E. *Synthesis* **1976**, 777–794. (b) Jung, M. E. *Tetrahedron* **1976**, *32*, 3–31.
9. For a transannular aldol condensation, see: Chai, K. B.; Sampson, P. *J. Org. Chem*. **1993**, *58*, 6807–6813.
10. For Robinson annulation reaction conditions, see: Stork, G.; Brizzolara, A.; Landesman, H.; Szmuszkovicz, J.; Terrell, R. *J. Am. Chem. Soc*. **1963**, *85*, 207–222.
11. Shimamoto, K.; Ishida, M.; Shinozaki, H.; Ohfune, Y. *J. Org. Chem*. **1991**, *56*, 4167–4176.
12. Schultz, A. G.; Lucci, R. D.; Fu, W. Y.; Berger, M. H.; Erhardt, J.; Hagmann, W. K. *J. Am. Chem. Soc*. **1978**, *100*, 2150–2162.
13. For aromatization procedures, see: (a) Bondon, D.; Pietrasanta, Y.; Pucci, B. *Tetrahedron Lett*. **1977**, 821–882. (b) Hirao, T.; Mori, M.; Ohshiro, Y. *J. Org. Chem*. **1990**, *55*, 358–360. (c) Paquette, L. A.; Thompson, R. C. *J. Org. Chem*. **1993**, *58*, 4952–4962. (d) Sharpless, K. B.; Lauer, R. F.; Teranishi, A. Y. *J. Am. Chem. Soc*. **1973**, *95*, 6137.