Available online at www.sciencedirect.com
ScienceDirect
Tetrahedron: Asymmetry
Tetrahedron: *Asymmetry* 17 (2006) 2260–2264

Asymmetric synthesis of 1-benzyl-2-((*S*)-2′,2′-dimethyl-1′,3′-dioxolan-4′-yl)-1*H*-pyrrole using chiral imines

David Díez,* Ana B. Antón, Pilar García, Marta G. Nuñez, Narciso M. Garrido, Rosalina F. Moro, Isidro S. Marcos, Pilar Basabe and Julio G. Urones

Dpto. de Química Orgánica, Facultad de Ciencias Quimicas, Universidad de Salamanca, 37008 Salamanca, Spain

Received 2 July 2006; accepted 5 July 2006
Available online 23 August 2006

Abstract—A new synthesis of chiral alkyl pyrroles and pyrrolines has been achieved in an easy straightforward way, using the addition of organometallics to chiral imines.
© 2006 Elsevier Ltd. All rights reserved.

1. Introduction

Pyrroles and pyrrolines are heterocycles present in many bioactive natural[1] and therapeutic compounds,[2] new organic materials[3] and anion binding agents.[3d] Monopyrrolic compounds are particularly important[4] due to their presence in ionophores as Routiennocin, **1**[5] while nucleus **2** is present in many alkaloids of the Senecio family of plants (Fig. 1).[6]

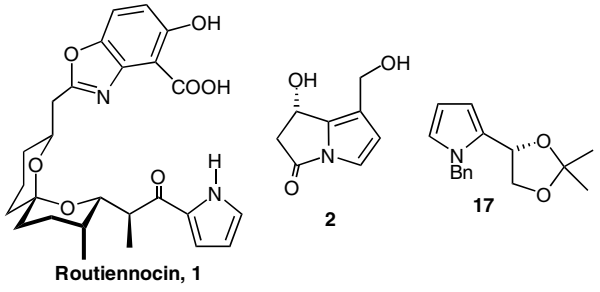


Figure 1.

Therefore many syntheses of pyrroles have been described,[7] although to the best of our knowledge, no synthesis of chiral 2-(1′-hydroxyalkyl) pyrroles has been reported. The addition of organometallic to chiral imines is a very well studied methodology,[8] that has been used by Reissig et al. for the synthesis of non-chiral pyrroles,[9a] and more recently reported the synthesis of pyrrole **17** as a side product in the synthesis of enantiopure amino polyols and pyrrolidines derivatives was reported.[9b] We have been interested in the addition of vinylsulfones to imines derived from (*R*)-glyceraldehyde for the synthesis of aminoacid derivatives, Figure 2.[10,11]

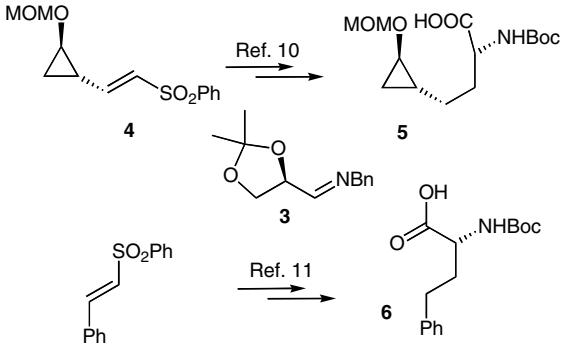


Figure 2.

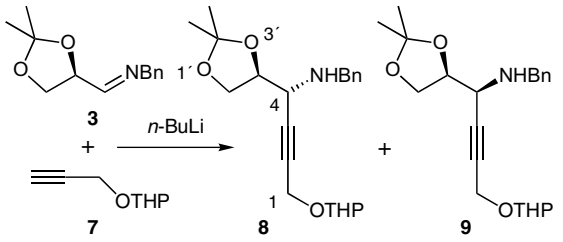
2. Results and discussion

The addition of the lithium anion of **7** to acetone has previously been used by us, for the synthesis of a variety of tetrahydropyran and tetrahydrofuran derivatives.[12]

* Corresponding author. Tel.: +34 923 294474; fax: +34 923 294574; e-mail: ddm@usal.es

0957-4166/$ - see front matter © 2006 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetasy.2006.07.008

Hence we decided to study the addition of this anion under different conditions[13] to imine **3** (Scheme 1).



Entry	Additive	T[a]/°C	Solvent	Yield	Ratio **8/9**
1	-	-20	THF	56	50 / 50
2	BF_3Et_2O	-20	THF	77	54 / 46
3	$CeCl_3$	-20	THF	45	10 / 90
4	$ZnMe_2$	50	Toluene	55	22 / 78

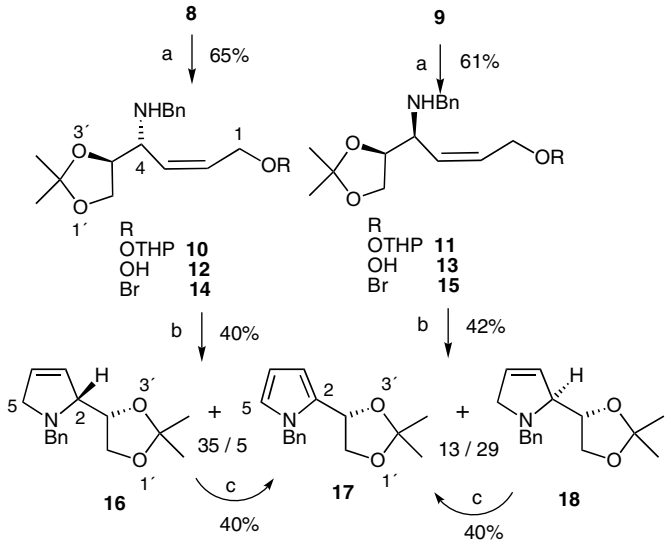
Scheme 1.

In our hands, the best ratio achieved was at −20 °C in THF as solvent and with the addition of $CeCl_3$ (entry 3), although in low yield. In order to determine the stereochemistry of compounds **8** and **9**, obtained in the addition reaction, they were separated by column chromatography and transformed into the known compounds.

When compounds **8** and **9** were hydrogenated using Lindlar catalyst, they gave the *cis*-olefins **10** and **11**, respectively, in good yield. Compounds **10** and **11** were deprotected under dilute conditions[14] to the corresponding alcohols **12** and **13**. These alcohols were submitted without purification, to a one-pot reaction. They were then treated separately with CBr_4 and PPh_3 in dichloromethane and when the reaction was complete as shown by TLC, an equivalent of Et_3N was added, to give a mixture of pyrroline **16** and pyrrole **17** from bromide **14** in a 35/5 ratio and pyrroline **18** and pyrrole **17** in a 29/13 ratio from bromide **15** in moderate yield for the three steps. Pyrroline **18** has previously been synthesized by Díaz-de-Villegas and Galvez et al.[15] and so the stereochemistry of the addition compounds to the imine **3** and pyrrolines **16** and **18** is confirmed. The stereochemistry of pyrrole **17** came from the starting material. Pyrrolines **16** and **18** were transformed separately to pyrrole **17** by treatment with DDQ in DCM. Pyrrole **17** was obtained as well without separation of pyrrolines that improve the yields. Although the synthesis of pyrrole **17** has been described previously as a side product,[9b] this methodology improves the yield and converts this compound into a chiral synthon that can be used in asymmetric synthesis (Scheme 2).

3. Conclusion

In conclusion a new methodology for the synthesis of chiral 2-substituted alkylpyrroles and pyrrolines has been opened. All compounds can be obtained in both enantiomeric forms, by choosing the appropriate starting material, adding more versatility to this synthesis. Further development using this methodology is ongoing.



Scheme 2. Reagents: (a) H_2, Lindlar catalyst, EtOAc, rt; (b) 1. TsOH, MeOH, 2. CBr_4, PPh_3, DCM, then NEt_3; (c) DDQ, DCM.

4. Experimental

4.1. General

Unless otherwise stated, all chemicals were purchased in the highest purity commercially available and were used without further purification. IR spectra were recorded on a AVATAR 370 FT-IR Thermo Nicolet spectrophotometer. ^1H and ^{13}C NMR spectra were performed in $CDCl_3$ and referenced to the residual peak of $CHCl_3$ at δ 7.26 ppm and δ 77.0 ppm, for ^1H and ^{13}C, respectively, using Varian 200 VX and Bruker DRX 400 instruments. Chemical shifts are reported in δ ppm and coupling constants (J) are given in hertz. MS and HRMS were performed in a QSTAR XL spectrometer using electrospray technique. Optical rotations were determined in a Perkin–Elemer 241 polarimeter in 1 dm cells. Diethyl ether, THF and benzene were distilled from sodium, and dichloromethane was distilled under argon from CaH_2.

4.2. Procedures of the addition reaction to imine 3

Additive: none. *n*-BuLi 1.6 M (27.4 mL, 43.8 mmol) was added to a solution of **7** (7.16 g, 51.1 mmol) in THF (100 mL) at −20 °C. After 10 min, imine **3** (3.20 g, 14.6 mmol) was added to the reaction flask via *cannula* as a solution in THF (29 mL). The reaction mixture was left to stir overnight at −20 °C → rt under Ar before the addition of saturated ammonium chloride solution (16 mL). The product was extracted into EtOAc (3×). The organic extracts were combined, washed with brine, dried over anhydrous Na_2SO_4, filtered and the solvent removed in vacuo. The resultant oil was submitted to flash silica column chromatography (hexane–EtOAc, 9:1) to yield 1.41 g (3.94 mmol, 27%) of **8** and 1.52 g (4.23 mmol, 29%) of **9**.

Additive: BF_3Et_2O. To a solution of compound **7** (1.14 g, 8.15 mmol) in THF (16.3 mL), *n*-BuLi 1.6 M (4.4 mL, 7.0 mmol) was slowly added at −20 °C under Ar with

stirring. After 10 min, the reaction mixture was cooled to −78 °C and BF_3Et_2O (0.9 mL, 7.0 mmol) was added to the solution and the mixture was stirred for 10 min. Imine **3** (510 mg, 2.33 mmol) was then added and the mixture stirred for 1 h at −78 °C before addition of NaOH 10% solution (12 mL). The product was extracted into Et_2O (3×). The organic extracts were combined, washed with brine, dried over anhydrous Na_2SO_4, filtered and the solvent was removed in vacuo. The resultant oil was submitted to flash silica column chromatography (hexane–EtOAc, 8:2) to yield 642 mg (1.78 mmol, 77%) of **8** and **9**.

Additive: $CeCl_3$. Cerium chloride (1.7 g, 6.9 mmol) was placed in a 100 mL flask and was heated with stirring at 140 °C in vacuo for 30 min and cooled. Dry THF (4 mL) was added with stirring under Ar and stirring was continued for 2 h. The resulted suspension was then cooled to −78 °C, and the previously formed organolithium compound (6.9 mmol) was added with stirring. After being kept at the same temperature for 10 min, imine **3** (500 mg, 2.3 mmol) in THF (4.6 mL) was added and the mixture stirred overnight at −78 °C → rt. The reaction mixture was then treated with saturated ammonium chloride solution, filtered through Celite and the product extracted into EtOAc (3×). The organic extracts were combined, washed with brine, dried over anhydrous Na_2SO_4, filtered and the solvent was removed in vacuo. The resultant oil was submitted to flash silica column chromatography (hexane–EtOAc, 8:2) to yield 371 mg (1.03 mmol, 45%) of **8** and **9**.

Additive: $ZnMe_2$. In a flask under an inert Ar atmosphere, alkyne **7** (881 mg, 5.7 mmol) was dissolved in anhydrous toluene (20 mL). A 2.0 M solution of $ZnMe_2$ in toluene (2.15 mL, 5.7 mmol) was then carefully added, and the resulting mixture was stirred at rt for 30 min. Imine **3** (500 mg, 2.3 mmol) was then added via *cannula* as a solution in toluene (3 mL), and the temperature was increased to 50 °C. The resulting solution was stirred for 24 h. The reaction was quenched with water. The aqueous phase was extracted with CH_2Cl_2 (3×), and the organic phase washed with brine and dried over anhydrous Na_2SO_4. The evaporation of the solvent under reduced pressure furnished the crude product, which was purified by flash column chromatography to yield 454 mg (1.27 mmol, 55%) of **8** and **9**.

4.2.1. Tetrahydropyranyl derivative of (*R*)-4-(benzylamino)-4-((*S*)-2′,2′-dimethyl-1′,3′-dioxolan-4′-yl)but-2-yn-1-ol, 8. $[\alpha]_D^{20} = +16.3$ (*c* 0.9, $CHCl_3$), IR (film) *v* (cm^{-1}): 3150–3600, 2940, 2865, 1453, 1373, 1263, 1197, 1127, 1067, 1021; ^1H NMR ($CDCl_3$, 200 MHz) δ (ppm): 1.10–1.95 (6H, m, 2H-2″, 2H-3″, 2H-4″), 1.34, 1.43 and 1.51 (6H, 3s, 2Me-2′), 3.42–3.61 (1H, m, H_A-5″), 3.80 and 4.05 (1H each, 2d, $J = 12.8$ Hz, –CH_2Ph), 3.76–3.94 (1H, m, H_B-5″), 3.94–4.14 (2H, m, 2H-5′), 4.15–4.24 (1H, m, H-4′), 4.27 (1H, d, $J = 4.4$ Hz, H-4), 4.34 (2H, s, 2H-1), 4.76–4.82 and 4.82–4.89 (1H, 2m, H-1″), 7.18–7.42 (5H, m, –CH_2*Ph*); ^{13}C NMR ($CDCl_3$, 50 MHz) δ (ppm): 19.0 and 19.2 (C-3″), 25.5 (C-4″), 26.6 (Me-2′), 30.4 (C-2″), 31.5 (Me-2′), 51.4 (–*C*H_2Ph), 51.9 (C-4), 54.4 (C-1), 61.9 and 62.0 (C-5″), 67.0 (C-5), 77.6 (C-4′), 81.3 (C-3), 83.8 (C-2), 96.6 (C-1″), 109.9 (C-2′), 127.3 (C_{para}–Ph), 128.5 and 128.6 (C_{ortho} and C_{meta}–Ph), 139.6 (C_{ipso}–Ph). MS, ESI: 382 $[M+Na]^+$, 360 $[M+H]^+$ 221; HRMS (ESI): calculated for $C_{21}H_{30}NO_4$, $[M+H]^+$: 360.2169; found 360.2152.

4.2.2. Tetrahydropyranyl derivative of (*S*)-4-(benzylamino)-4-((*S*)-2′,2′-dimethyl-1′,3′-dioxolan-4′-yl)but-2-yn-1-ol, 9. $[\alpha]_D^{20} = -59.0$ (*c* 1.25, $CHCl_3$). IR (film) *v* (cm^{-1}): 3150–3600, 2985, 2940, 2870, 1735, 1669, 1458, 1378, 1263, 1212, 1157, 1087, 1026. ^1H NMR ($CDCl_3$, 200 MHz) δ (ppm): 1.32 (6H, s, 2Me-2′), 1.42–1.79 (6H, m, 2H-2″, 2H-3″, 2H-4″), 3.42–3.54 (2H, m, H-4, H_A-5″), 3.83 and 4.07 (1H each, 2d, $J = 13.2$ Hz, –CH_2Ph), 3.78–3.88 (1H, m, H_B-5″), 3.92 (1H, dd, $J = 5.6$ and 8.4 Hz, H_A-5′), 4.02–4.08 (1H, m, H_B-5′), 4.15–4.26 (1H, m, H-4′), 4.30 (2H, s, H-1), 4.76–4.86 (1H, m, H-1″), 7.22–7.36 (5H, m, –CH_2*Ph*). ^{13}C NMR ($CDCl_3$, 50 MHz) δ (ppm): 19.3 (C-3″), 25.5 (C-4″), 26.9 (2Me-2′), 30.4 (C-2″), 50.8 (–*C*H_2Ph), 52.3 (C-4), 54.3 (C-1), 62.2 (C-5″), 67.1 (C-5′), 77.5 (C-4′), 82.1 (C-3), 82.6 (C-2), 96.9 (C-1″), 110.3 (C-2′), 127.6 (C_{para}–Ph), 128.7 (C_{meta}–Ph), 128.8 (C_{ortho}–Ph), 138.4 (C_{ipso}–Ph). MS, ESI: 382 $[M+Na]^+$, 360 $[M+H]^+$. HRMS (ESI): calculated for $C_{21}H_{30}NO_4$, $[M+H]^+$: 360.2169; found: 360.2168.

4.2.3. Tetrahydropyranyl derivative of (*R*,*Z*)-4-(benzylamino)-4-((*S*)-2′,2′-dimethyl-1′,3′-dioxolan-4′-yl)but-2-en-1-ol, 10. To a solution of **8** (367 mg, 1.03 mmol) in dry ethyl acetate (5.2 mL) was added the Lindlar catalyst (142 mg). The mixture was stirred for 10 min before the addition of quinoline (115 μL, 1.13 mmol). The mixture was left to stir under hydrogen for 24 h. It was then filtered through Celite and the solvent was evaporated in vacuo. The product was purified by column chromatography (hexane/EtOAc 9:1) to yield 241 mg (0.67 mmol, 65%) of **10**. $[\alpha]_D^{20} = +6.4$ (*c* 1.38, $CHCl_3$). IR (film) *v* (cm^{-1}): 3200–3600, 2990, 2935, 2875, 1725, 1684, 1448, 1383, 1258, 1202, 1127. ^1H NMR ($CDCl_3$, 200 MHz) δ (ppm): 1.33 (3H, s, Me-2′), 1.40 (3H, s, Me-2′), 1.38–1.85 (6H, m, 2H-2″, 2H-3″, 2H-4″), 2.45 (1H, br s, N*H*), 3.42–3.48 (1H, m, H_A-5″), 3.62 (1H, dd, $J = 4.6$ and 9.6 Hz, H-4), 3.64, 3.66 and 3.90 (2H, 3d, $J = 13.4$ Hz, –CH_2Ph), 3.75–3.85 (1H, m, H_B-5″), 3.92–4.05 (2H, m, 2H-5′), 4.16 (2H, d, $J = 6.9$ Hz, H-1), 4.16–4.32 and 4.26–4.32 (1H, 2m, H-4′), 4.55–4.60 (1H, m, 1H-1″), 5.44 (1H, dd, $J = 9.7$ and 11.2 Hz, H-3), 5.90 (1H, dt, $J = 6.9$ and 12.1 Hz, H-2), 7.19–7.35 (5H, m, –CH_2*Ph*). ^{13}C NMR ($CDCl_3$, 50 MHz) δ (ppm): 19.3 (C-3″), 25.0 (Me-2′), 25.3 (C-4″), 26.2 (Me-2′), 30.5 (C-2″), 50.7 (–*C*H_2Ph), 55.6 (C-4), 62.1 (C-1), 63.1 and 63.2 (C-5″), 66.0 (C-5′), 77.8 (C-4′), 98.1 and 98.2 (C-1″), 109.0 (C-2′), 127.0 (C_{para}–Ph), 128.1 (C_{meta}–Ph), 128.4 (C_{ortho}–Ph), 130.5 (C-3), 131.1 and 131.2 (C-2), 139.7 (C_{ipso}–Ph). MS, ESI: 362 $[M+H]^+$, 278. HRMS (ESI): calculated for $C_{21}H_{32}NO_4$, $[M+H]^+$: 362.2326; found: 362.2335.

4.2.4. Tetrahydropyranyl derivative of (*S*,*Z*)-4-(benzylamino)-4-((*S*)-2′,2′-dimethyl-1′,3′-dioxolan-4′-yl)but-2-en-1-ol, 11. To a solution of **9** (300 mg, 0.84 mmol) in dry ethyl acetate (8.4 mL) was added the Lindlar catalyst (117 mg). The mixture was stirred for 10 min before the addition of quinoline (108 μL, 0.92 mmol). The mixture was left to stir under hydrogen for 20 h. It was then filtered through Celite

and the solvent was evaporated in vacuo. The product was purified by column chromatography (hexane/EtOAc 8:2) to yield 185 mg (0.51 mmol, 61%) of **11**. $[\alpha]_D^{20} = -13.9$ (*c* 1.02, $CHCl_3$). IR (film) *v* (cm^{-1}): 3327, 2984, 2940, 1496, 1455, 1370, 1259, 1211, 1157, 1119, 1063, 1027, 905, 849, 815, 738. ^1H NMR ($CDCl_3$, 200 MHz) δ (ppm): 1.32 (3H, s, Me-2′), 1.35 and 1.36 (3H, 2s, Me-2′), 1.47–1.87 (6H, m, 2H-2″, 2H-3″, 2H-4″), 2.20 (1H, br s, N*H*), 3.42–3.53 (2H, m, H-4 and H_A-5″), 3.61, 3.62 and 3.88 (2H, 3d, $J = 13.4$ Hz, –CH_2Ph), 3.65–3.75 (1H, m, H_A-5′), 3.77–3.85 (1H, m, H_B-5″), 3.90–4.07 (3H, m, H_B-5′ and H-1), 4.15–4.20 and 4.23–4.30 (1H, 2m, H-4′), 4.57–4.59 (1H, m, H-1″), 5.38 (1H, t, $J = 10.6$ Hz, H-3), 5.86 (1H, dt, $J = 6.9$ and 12.2 Hz, H-2), 7.18–7.36 (5H, m, –CH_2Ph). ^{13}C NMR ($CDCl_3$, 50 MHz) δ (ppm): 19.4 (C-3″), 25.4 (C-4″), 25.5 (Me-2′), 26.8 (Me-2′), 30.5 (C-2″), 50.8 (–*C*H_2Ph), 57.6 (C-4), 62.1 and 62.2 (C-1), 63.2 and 63.4 (C-5″), 66.6 (C-5′), 78.2 (C-4), 98.2 and 98.3 (C-1″), 109.5 (C-2′), 126.9 (C_{para},–Ph), 128.1 (C_{meta}–Ph), 128.3 (C_{ortho}–Ph), 130.9 and 131.0 (C-3), 131.4 and 131.5 (C-2′), 140.0 (C_{ipso}–Ph). MS, ESI: 362 $[M+H]^+$, 278. HRMS (ESI): calculated for $C_{21}H_{32}NO_4$, $[M+H]^+$: 362.2326; found: 362.2323.

4.2.5. (*R*,*Z*)-4-(Benzylamino)-4-((*S*)-2′,2′-dimethyl-1′,3′-dioxolan-4′-yl)but-2-en-1-ol, 12. To a solution of **10** (113 mg, 0.31 mmol) in MeOH (11.4 mL) was added a catalytic amount of *p*-toluensulfonic acid monohydrate. The mixture was left to stir for 1 h. The solution was then diluted with EtOAc, and washed with a solution of sodium bicarbonate (5%), water and saturated brine. The organic phase was dried with anhydrous sodium sulfate, filtered and the solvent removed in vacuo. The product was purified by column chromatography (hexane–EtOAc 6:4) to yield 40 mg (0.14 mmol, 46%) of **12**. Yield was improved when diol **12** was not submitted to chromatography. $[\alpha]_D^{20} = -99.2$ (*c* 1.27, $CHCl_3$). IR (film) *v* (cm^{-1}): 3100–3600, 2986, 2926, 2871, 1682, 1463, 1370, 1266, 1211, 1151, 1030. ^1H NMR ($CDCl_3$, 200 MHz) δ (ppm): 1.34 (3H, s, Me-2′), 1.41 (3H, s, Me-2′), 2.60 (2H, br s, O*H* and N*H*), 3.51–3.61 (1H, m, H-4), 3.67 and 3.89 (1H each, 2d, $J = 13.2$ Hz, –CH_2Ph), 3.78–3.94 (1H, m, H_A-5′), 4.07 (2H, d, $J = 6.4$ Hz, 2H-1), 4.01–4.16 (2H, m, H-4′, H_B-5′), 5.45 (1H, dd, $J = 9.2$ and 11.4 Hz, H-3), 5.98 (1H, dt, $J = 6.6$ and 11.0 Hz, H-2), 7.22–7.35 (5H, m, –CH_2Ph). ^{13}C NMR ($CDCl_3$, 50 MHz) δ (ppm): 25.3 (Me-2′), 26.5 (Me-2′), 51.1 (–*C*H_2Ph), 56.7 (C-4), 58.8 (C-1), 67.1 (C-5′), 77.3 (C-4′), 109.6 (C-2′), 127.5 (C_{para}–Ph), 128.4 (C_{meta}–Ph), 128.7 (C_{ortho}–Ph), 131.5 (C-3), 133.7 (C-2), 139.9 (C_{ipso}–Ph). MS, ESI: 278 $[M+H]^+$, 220. HRMS (ESI): calculated for $C_{16}H_{24}NO_3$, $[M+H]^+$: 278.1751; found: 278.1754.

4.2.6. (*S*,*Z*)-4-(Benzylamino)-4-((*S*)-2′,2′-dimethyl-1′,3′-dioxolan-4′-yl)but-2-en-1-ol, 13. To a solution of **11** (148 mg, 0.41 mmol) in MeOH (15 mL) was added a catalytic amount of *p*-toluensulfonic acid monohydrate. The mixture was left to stir for 45 min. The solution was then diluted with EtOAc, and washed with a solution of sodium bicarbonate (5%), water and saturated brine. The organic phase was dried with anhydrous sodium sulfate, filtered and the solvent was removed in vacuo. The product was purified by column chromatography (hexane–EtOAc 6:4) to yield 63.5 mg (0.23 mmol, 56%) of **13**. The yield improved when diol **13** was not submitted to chromatography. $[\alpha]_D^{20} = -0.7$ (*c* 0.67, $CHCl_3$). IR (film) *v* (cm^{-1}): 3600–3100, 2986, 2921, 2866, 1463, 1381, 1216, 1079. ^1H NMR ($CDCl_3$, 200 MHz) δ (ppm): 1.32 (3H, s, Me-2′), 1.34 (3H, s, Me-2′), 3.35–3.60 (2H, br s, N*H* and O*H*), 3.42 (1H, t, $J = 8.4$ Hz, H-4), 3.95 and 3.65 (1H each, 2d, $J = 13.2$ Hz, –CH_2Ph), 3.70 (1H, dd, $J = 5.8$ and 8.4 Hz, H_A-5′), 3.98 (1H, dd, $J = 6.2$ and 8.4 Hz, H_B-5′), 4.18 (2H, d, $J = 5.4$ Hz, H-1), 4.05–4.26 (1H, m, 1H-4′), 5.33–5.43 (1H, m, H-3), 5.86 (1H, dt, $J = 5.4$ and 11.8 Hz, H-2), 7.26–7.34 (5H, m, –CH_2Ph). ^{13}C NMR ($CDCl_3$, 50 MHz) δ (ppm): 25.7 (Me-2′), 27.1 (Me-2′), 50.9 (–*C*H_2Ph), 58.3 (C-4), 59.8 (C-1), 66.9 (C-5′), 78.4 (C-4′), 109.9 (C-2′), 127.5 (C_{para}–Ph), 128.4 (C-3), 128.8 (C_{ortho} and C_{meta}–Ph), 135.3 (C-2), 139.5 (C_{ipso}–Ph).

4.2.7. (*S*)-1-Benzyl-2,5-dihydro-2-((*S*)-2′,2′-dimethyl-1′,3′-dioxolan-4′-yl)-1*H*-pyrrole, 16. To a solution of **12** (68.3 mg, 0.25 mmol) in DCM (1.7 mL) were added PPh_3 (70.8 mg, 0.27 mmol) and CBr_4 (89.6 mg, 0.27 mmol). The mixture was left to stir for 30 min before the addition of Et_3N (105 μL, 0.75 mmol). The solution was stirred for 2 h, then diluted with DCM and washed with an HCl (2 M) solution (2×), sodium bicarbonate (5%) solution (2×), water and saturated brine. The organic phase was dried with anhydrous sodium sulfate, filtered and the solvent removed in vacuo. The product was purified by column chromatography (hexane–EtOAc 8:2) to yield 3.2 mg (0.012 mmol, 5%) of **17** and 22.7 mg (0.09 mmol, 35%) of **16**. $[\alpha]_D^{20} = +138.4$ (*c* 0.41, $CHCl_3$). IR (film) *v* (cm^{-1}): 2990, 2935, 2870, 2789, 1378, 1217, 1157, 1067, 966. ^1H NMR ($CDCl_3$, 200 MHz) δ (ppm): 1.34 (3H, s, Me-2′), 1.44 (3H, s, Me-2′), 3.25 (1H, ddt, $J = 2.2$, 2.2, 4.0 and 14 Hz, H_A-5), 3.66 and 4.14 (1H each, 2d, $J = 13.6$ Hz, –CH_2Ph), 3.60–3.67 (1H, m, H_B-5), 3.82 (1H, dd, $J = 6.2$ and 8.2 Hz, H_A-5′), 3.87–3.98 (1H, m, H-2), 4.00 (1H, dd, $J = 6.6$ and 8.0 Hz, H_B-5′), 4.06–4.20 (1H, m, H-4′), 5.66–5.72 (1H, m, H-3), 5.85–5.89 (1H, m, H-4), 7.23–7.33 (5H, m, –CH_2Ph). ^{13}C NMR ($CDCl_3$, 50 MHz) δ (ppm): 25.1 (Me-2′), 26.7 (Me-2′), 59.8 (–*C*H_2Ph), 61.0 (C-5), 65.9 (C-5′), 72.6 (C-2), 77.2 (C-4′), 109.4 (C-2′), 127.0 (C-3 and C_{para}–Ph), 128.6 (C_{ortho} and C_{meta}–Ph), 129.8 (C-4), 140.2 (C_{ipso}–Ph). MS, ESI: 260$[M+H]^+$, 202. HRMS (ESI): calculated for $[M+H]^+$: 260.1645; found: 260.1655.

4.2.8. (*R*)-1-Benzyl-2,5-dihydro-2-((*S*)-2′,2′-dimethyl-1′,3′-dioxolan-4′-yl)-1*H*-pyrrole, 18. To a solution of **13** (106.6 mg, 0.38 mmol) in DCM (2.5 mL) was added PPh_3 (109.6 mg, 0.42 mmol) and CBr_4 (138.8 mg, 0.42 mmol). The mixture was left to stir for 30 min before the addition of Et_3N (160 μL, 1.14 mmol). The solution was stirred overnight, then diluted with DCM and washed with a HCl (2 M) solution (2×), sodium bicarbonate (5%) solution (2×), water and saturated brine. The organic phase was dried with anhydrous sodium sulfate, filtered and the solvent removed in vacuo. The product was purified by column chromatography (hexane–EtOAc 8:2) to yield 12.5 mg (0.048 mmol, 13%) of **17** and 28.2 mg (0.11 mmol, 29%) of **18**. $[\alpha]_D^{20} = -73.0$ (*c* 0.63, $CHCl_3$). ^1H NMR ($CDCl_3$, 200 MHz) δ (ppm): 1.34 (3H, s, Me-2′), 1.39

(3H, s, Me-2′), 3.22 (1H, dddd, $J = 2.1$, 2.1, 4.2, 14.7 Hz, H_A-5), 3.64 and 4.19 (1H each, 2d, $J = 13.8$ Hz, –CH_2Ph), 3.71 (1H, dddd, $J = 1.8$, 3.6, 5.4, 14.7 Hz, H_B-5), 3.87–3.97 (3H, m, H-2 and 2H-5′), 4.09–4.16 (1H, m, H-4′), 5.68–5.72 (1H, m, H-3), 5.75–5.82 (1H, m, H-4), 7.19–7.38 (5H, m, –CH_2*Ph*). ^{13}C NMR ($CDCl_3$, 50 MHz) δ (ppm): 25.2 (Me-2′), 26.5 (Me-2′), 60.9 (C-5), 66.2 (C-5′), 71.94 (C-2), 79.16 (C-4′), 108.9 (C-2′), 126.8 (C-3), 127.8 (C-4), 128.3 (C_{ortho} and C_{meta}–Ph), 128.9 (C_{para}–Ph), 140.2 (C_{ipso}–Ph).

4.2.9. 1-Benzyl-2-((*S*)-2′,2′-dimethyl-1′,3′-dioxolan-4′-yl)-1*H*-pyrrole, 17. To a solution of **16** and **18** (41.4 mg, 0.16 mmol) in DCM (1 mL) was added DDQ (36.3 mg, 0.16 mmol) under Ar at rt. The mixture was stirred for 30 min. Solvent was then evaporated under reduced pressure. The product was purified by column chromatography (hexane–EtOAc 9:1) to yield 16.5 mg (0.064 mmol, 40%) of **17**. $[\alpha]_D^{20} = -20.7$ (*c* 0.83, $CHCl_3$). IR (film) ν (cm^{-1}): 2990, 2920, 2850, 1448, 1368, 1303, 1212, 1162, 1052. ^{1}H NMR ($CDCl_3$, 200 MHz) δ (ppm): 1.38 (3H, s, Me-2′), 1.41 (3H, s, Me-2′), 3.94–4.12 (2H, m, 2H-5′), 4.99 (1H, t, $J = 6.6$ Hz, H-4′), 5.14 and 5.27 (1H each, 2d, $J = 16.2$ Hz, –CH_2Ph), 6.13–6.22 (2H, m, H-3 and H-4), 6.68–6.71 (1H, m, H-5), 7.03–7.08 (2H, m, H_{meta}–Ph), 7.20–7.38 (3H, m, H_{ortho} and H_{para}–Ph). ^{13}C NMR ($CDCl_3$, 50 MHz) δ (ppm): 26.2 (Me-2′), 26.9 (Me-2′), 50.9 (–*C*H_2Ph), 68.6 (C-5′), 70.6 (C-4′), 107.8 (C-3 and C-4), 109.7 (C-2′), 123.7 (C-5), 126.8 (C_{meta}–Ph), 127.7 (C_{para}–Ph), 128.9 (C_{ortho}–Ph), 129.3 (C-2), 138.4 (C_{ipso}–Ph). MS, ESI: 280 $[M+Na]^+$, 245, 200, 149. HRMS (ESI): calculated for $[M+Na]^+$: 280.1308; found: 280.1311.

Acknowledgements

Financial support for this work came from the E.F.S.; Spanish MEC (CTQ2005-06813/BQU) and Junta de Castilla y León (Spain) (SA045A05). The authors also thank Dr. A. M. Lithgow for the NMR spectra and Dr. César Raposo for the mass spectra. M.G.N. is grateful for a FPU doctoral fellowship of the Spanish MEC.

References

1. (a) Gribble, G. W. In *Comprehensive Heterocyclic Chemistry II*; Katrizky, A. R., Rees, C. W., Scriven, E. S. V., Eds.; Pergamon Press: Oxford, 1996; Vol. 2, pp 207–257; (b) Le Quesne, P. W.; Dong, Y.; Blythe, T. A. *Alkaloids: Chem. Biol. Perspect.* **1999**, *13*, 237–287; (c) Janosik, T.; Bergman, J. In *Progress in Heterocyclic Chemistry*; Gribble, G. W., Joule, J. A., Eds.; Pergamon: Amsterdam, 2003; Vol. 15, pp 140–166; (d) Feldman, K. S.; Saunders, J. C.; Wrobleski, M. L. *J. Org. Chem.* **2002**, *67*, 7096; (e) Bellina, F.; Rossi, R. *Tetrahedron* **2006**, *62*, 7213.
2. (a) O'Toole-Colin, K.; Getzel, A.; Argenti, A.; Evans, M. A.; Smith, D. C.; Dalglish, G. A.; Rifat, S.; Wilson, D. L.; Taylor, B. M.; Miott, U.; Glersaye, J.; Lam, K. S.; McCranor, B. J.; Berkowitz, J. D.; Miller, R. B.; Lukens, J. R.; Krumpe, K.; Gupton, J. T.; Burnham, B. S. *Molecules* **2004**, *9*, 135, and references cited therein; (b) Huffman, J. W. *Curr. Med. Chem.* **1999**, *6*, 705–720.
3. (a) Lee, C. F.; Yang, L. M.; Hwu, T. Y.; Feng, A. S.; Tseng, J. C.; Luh, T. Y. *J. Am. Chem. Soc.* **2000**, *122*, 4992; (b) Domingo, V. M.; Aleman, C.; Brillas, E.; Julia, L. *J. Org. Chem.* **2001**, *66*, 4058; (c) Curran, D.; Grimshaw, J.; Perera, S. D. *Chem. Soc. Rev.* **1991**, *20*, 391; (d) Sessler, J. L.; Camiolo, S.; Gale, P. A. *Coord. Chem. Rev.* **2003**, *240*, 17.
4. Gossauer, A. Monopyrrolic Natural Compounds Including Tetramic Acid Derivatives. In *Forstschritte der Chemie Organischer Naturstoffe*; Herz, W., Falk, H., Kirby, G. W., Eds.; Springer: Wien, 2003; Vol. 86, pp 1–188.
5. Díez-Martín, D.; Kotecha, R. N.; Ley, S. V.; Mantegani, S.; Menéndez, J. C.; Organ, H. M.; White, A. D. *Tetrahedron* **1992**, *48*, 7899.
6. (a) McNab, H.; Thornley, C. *J. Chem. Soc., Perkin Trans. 1* **2000**, 3584; (b) Jakupovic, J.; Grenz, M.; Bohlmann, F.; Niemeyer, H. M. *Phytochemistry* **1991**, *30*, 2691.
7. (a) Bellur, E.; Laanger, P. *Tetrahedron Lett.* **2006**, *47*, 2151, and references cited therein; (b) Sundber, R. J. In *Comprehensive Heterocyclic Chemistry II*; Katrizky, A. R., Rees, C. W., Scriven, E. S. V., Eds.; Pergamon Press: Oxford, 1996; Vol. 2, pp 119–206; (c) Yang, Q.; Li, X.-Y.; Xiao, W.-J. P. *Tetrahedron Lett.* **2006**, *47*, 3893.
8. (a) Badorrey, R.; Cativiela, C.; Díaz-de-Villegas, M. D.; Gálvez, J. A. *Synthesis* **1997**, 747; (b) Badorrey, R.; Cativiela, C.; Díaz-de-Villegas, M. D.; Gálvez, J. A. *Tetrahedron* **1997**, *53*, 1411; (c) Badorrey, R.; Cativiela, C.; Díaz-de-Villegas, M. D.; Gálvez, J. A. *Tetrahedron* **2002**, *58*, 341; (d) Badorrey, R.; Cativiela, C.; Díaz-de-Villegas, M. D.; Díez, R.; Gálvez, J. A. *Eur. J. Org. Chem.* **2003**, 2268; (e) Bloch, R. *Chem. Rev.* **1998**, *98*, 1407, and references cited therein.
9. (a) Amombo, M. O.; Hausherr, A.; Reissig, H.-U. *Synlett* **1999**, 1871; (b) Pulz, R.; Schade, W.; Reissig, H.-U. *Synlett* **2003**, 405.
10. Díez, D.; García, P.; Moro, R. F.; Marcos, I. S.; Basabe, P.; Garrido, N. M.; Broughton, H. B.; Urones, J. G. *Synthesis* **2005**, 3327.
11. Díez, D.; García, P.; Marcos, I. S.; Basabe, P.; Garrido, N. M.; Broughton, H. B.; Urones, J. G. *Tetrahedron* **2005**, *61*, 11641.
12. Díez, D.; Marcos, I. S.; Basabe, P.; Romero, R. E.; Moro, R. F.; Lumeras, W.; Rodriguez, L.; Urones, J. G. *Synthesis* **2001**, 1013, and references cited therein.
13. (a) Wada, M.; Sakurai, Y.; Akiba, K.-Y. *Tetrahedron Lett.* **1984**, *25*, 1083; (b) Imamoto, T.; Sugiura, Y.; Takiyama, N. *Tetrahedron Lett.* **1984**, *25*, 4233; (c) Zani, L.; Alesi, S.; Cozzi, P. G.; Bolm, C. *J. Org. Chem.* **2006**, *71*, 1558.
14. Piatek, P.; Gruza, M. M.; Jurczak, J. *Tetrahedron Asymmetry* **2001**, *12*, 1763.
15. Badorrey, R.; Cativiela, C.; Díaz-de-Villegas, M. D.; Díez, R.; Gálvez, J. A. *Tetrahedron Lett.* **2004**, *45*, 719, and personnal communication.