Tetrahedron Letters,Vol.30,No.33,pp 4371-4374,1989 0040-4039/89 $3.00 + .00
Printed in Great Britain Pergamon Press plc

FIRST TOTAL SYNTHESIS OF (-)-α-CONIDENDRIN

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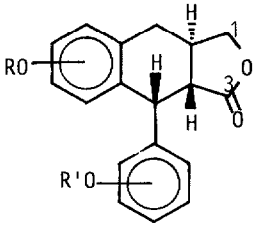
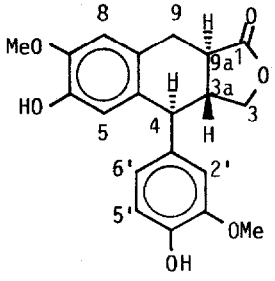
Summary : Regioselective introduction of a benzoxy group, in the benzylic position of the β-benzyl-γ-butyrolactone (R)-(+)-**8**, was achieved by treatment with NBS followed with benzyl alcohol. α-Alkylation of the lithium enolate of the resulting intermediate **11**, with O-benzylvanillyl bromide **5**, gave the trans disubstituted lactone **13**. Catalytic hydrogenolysis (Pd-C) of **13** selectively split the aryl benzyl ether linkage, thus giving the compound **14**. Intramolecular Friedel-Crafts cyclisation of the latter, using the benzoxy group as the leaving group, was induced with $BF_3.Et_2O$ and afforded high yields of (-)-α-conidendrin **2**.

Most lactonic aryltetralin lignans, such as podophyllotoxin and peltatins, have the same general structure **1**, in which the carbonyl group is in the 3 position. The "retrolignan" (-)-α-conidendrin **2** has a highly exceptional structure, inasmuch as the lactonic carbonyl lies in 1 position. Some years ago, a paper[1] from our laboratory described the first total synthesis of racemic α-conidendrin **2**, which involved as the key-step a Michael addition of the dithian anion **3** to butenolide **4**, followed by α-alkylation with O-benzylvanillyl bromide **5**. Hydrolysis of the thioketal group of the resulting trans disubstituted γ-butyrolactone intermediate, followed by $NaBH_4$ reduction of the ketonic carbonyl, intramolecular Friedel-Crafts cyclisation (brought about with CF_3CO_2H), and finally catalytic hydrogenolysis of both benzyl ether groups, afforded (±)-α-conidendrin **2**. This reaction scheme cannot be applied to a total synthesis of optically active α-conidendrin **2**, without introducing important modifications which are far from being obvious in any case. We describe now a total synthesis of natural (-)-conidendrin **2**, following an original reaction scheme which could be applied in theory to all retrolignans, and in both enantiomeric forms.

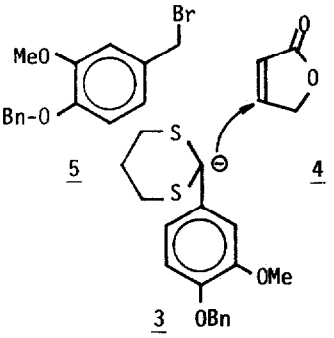
Racemic methyl α-vanillylhemisuccinate (R, S)-**6** was resolved by means of (R)-(+)-α-methylbenzylamine, thus affording (R)-(+)-**6** as previously described.[2] Calcium borohydride reduction of the latter gave the lactone (R)-(+)-**7**, m.p. 119-120°C and $[\alpha]_D^{22}$ +10.5° (c 1, $CHCl_3$).[2] Protection of the phenol group of (R)-(+)-**7** was carried out using Me_3SiCl (1.5 equ.) in CH_2Cl_2/pyridine (8:1 v/v) at room temperature for 1 h 20 min. The silyl ether (R)-**8** was thus obtained as a colourless oil in quantitative yield, and was used in the next step without purification. The compound (R)-**8** was treated with N-bromosuccinimide (1.1 equ.) in the presence of benzoyl peroxide in refluxing CCl_4 for 2 h.[3] Evaporation of the solvent under reduced pressure gave a residue which contained succinimide and presumably the unstable benzylic bromide **9**. This residue was dissolved in a mixture of CH_2Cl_2 and ether (4:5 v/v) and was treated with excess benzyl alcohol (ca. 4 equ.) for 48 h at room temperature, in the total absence of any basic reagent. The reaction mixture was then washed with 1N HCl and was concentrated under reduced pressure, thus affording an oil which solidified on trituration under cyclohexane. This solid was chromatographed over silica gel using



1

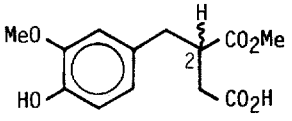


2

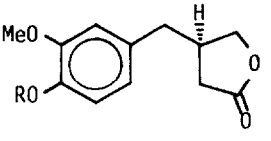


3 4 5

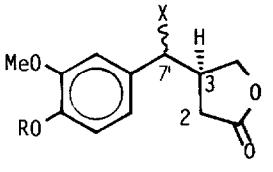
Bn = $PhCH_2$



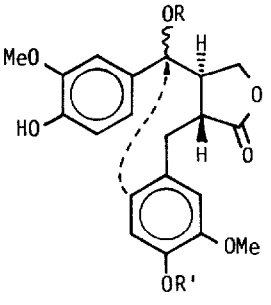
(R, S)-6
(R)-(+)-6, H-2α



(R)-(+)-7 R = H
(R)-8 R = Me_3Si



9 R = H ; X = Br
10 R = H ; X = BnO
11 R = Me_3Si ; X = BnO
12 R = Bn ; X = BnO



13 R = R' = Bn
14 R = Bn ; R' = H
15 R = R' = H

Reaction Scheme :

(R)-(+)-6 ⟶ (R)-(+)-7 ⟶ (R)-8 ⟶ 9

9 ⟶ 10 ⟶ 11 ⟶ 13 ⟶ 14 ⟶ 2

cyclohexane-ether (6:4 v/v) for the elution, and gave the benzoxy derivative **10** as a crystalline mixture of epimers, m.p. 135.5-136.5°C (ether), $[\alpha]_D^{22}$ +122° (c 1, CH_2Cl_2) and in 56% yield.[4] The undecoupled ^{13}C NMR spectrum of racemic **10**[5] in $CDCl_3$ exhibited two doublets at δ 82.0 and δ 81.4 ppm, corresponding to the C-7' atoms of both epimers and in the ratio 7:3. Protection of the phenol group of **10** was achieved using Me_3SiCl (1.5 equ.) in CH_2Cl_2/pyridine (8:1 v/v) at room temperature for 1 h 30 min. The resulting silyl ether **11** was obtained as a colourless oil in quantitative yield and was used in the next step without purification. The intermediate **11** was treated with lithium hexamethyldisilazide (1.5 equ.) in THF at -78°C, followed by the slow addition of the benzylic bromide **5**[6] in THF. After stirring for 6 h at -78°C, the mixture was acidified with 1N HCl. Chromatography of the reaction product over silica gel using toluene/AcOEt (95:5 v/v) for the elution, afforded the amorphous α,β-trans disubstituted lactone **13**, $[\alpha]_D$ +62.9° (c 0,9, $CHCl_3$) and in 72% yield.[7] It is worth mentioning that the O-dibenzyl derivative **12**, m.p. 110-115°C, deriving from racemic **10**[5] could not be alkylated by the benzylic bromide **5**, presumably because of steric hindrance.

The compound **13** was hydrogenated under a pressure of 3 bars in 95% ethanol and in the presence of 10% Pd-C, for 16 h at room temperature. Under these conditions, the hydrogenolysis of the aryl benzyl ether linkage of **13** was achieved with very good selectively, thus affording the monobenzoxy intermediate **14**, m.p. 148-149.5°C, $[\alpha]_D$ +51° (c 1, $CHCl_3$), and in 93% yield (crude).[8] TLC examination revealed that the compound **14** was contaminated in the crude state by trace amounts of a more polar substance, probably hydroxymatairesinol **15**. The compound **14** was next treated with $BF_3.Et_2O$ (ca. 3 equ.) in CH_2Cl_2 at room temperature for 40 min. Under these experimental conditions, the benzoxy group of **14** proved to be an excellent leaving group for intramolecular Friedel-Crafts alkylation, since (-)-α-conidendrin **2** was thus obtained as expected and in 94% yield, having m.p. 242°C (CH_2Cl_2) and $[\alpha]_D^{25}$ -52.5° (c 1.05, acetone). Lit.[9] m.p. 256°C (ethanol) and $[\alpha]_D$ -54.5° (c 4, acetone). Treatment of (-)-α-conidendrin **2** with excess Ac_2O in pyridine for 3 h under reflux gave the corresponding O-diacetyl derivative, m.p. 126-128°C ($CHCl_3/Et_2O$) and m.p. 221-223°C (EtOH).[10] Lit.[11a] m.p. 220-222°C (EtOH). This compound exhibited IR and ^1H NMR data identical with those reported for racemic O-diacetyl-α-conidendrin prepared by another route.[1,10]

Consistent IR and ^1H NMR data were obtained for all the compounds described in this paper. Satisfactory elemental analyses were obtained for the compounds (±)-**10**,[4] (+)-**13** and (+)-**14**.

Conclusion

We have described an efficient synthesis of (-)-α-conidendrin **2**, following a scheme which could be applied to all lactonic aryltetralin lignans of the "retro" series. (-)-α-Conidendrin **2** was obtained in eight steps from the readily available, optically active, hemisuccinic ester **6**. The present scheme involves two critical key-steps, i) the selective introduction of a benzoxy group in the benzylic position of the β-benzyl-γ-butyrolactone **8**, and ii) the internal Friedel-Crafts cyclisation of the intermediate **14**, using the benzoxy group as the leaving group.

Since (±)-β-conidendrin and methyl (±)-α and (±)-β-conidendrals [11] were obtained from (±)-O-dibenzyl-α-conidendrin,[1] the present work represents a formal total synthesis of the above compounds in optically active form.

References and notes

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2. E. BROWN and A. DAUGAN, Heterocycles, 1987, 26, 1169.
3. T. ISHIGURO, H. MIZUGUCHI, K. TOMIOKA and K.KOGA, Chem. Pharm. Bull. 1985, 33, 609.
4. Spectral data of (±)-**10**.[5] IR (CH_2Cl_2, film) νmax : 1772 (C=O) and 1602 cm^{-1}. ^1H NMR ($CDCl_3$) δ(ppm) : 7.4 (s, 5) aryl H ; 7.02 (d, J = 8 Hz, 1) aryl H ; 6,90 (m, 2) aryl H ; 6.0 (wide s, 1) OH ; 4.75-4.0 (m, 5) CH_2O, CH_2OCO and H-7' ; 3.92 (s, 3) OCH_3 ; 3.1-2.5 (m, 2) H-3 and H-2(A) ; 2.25 (dd, J_{AB} = 7Hz, $J_{2(B)-3}$ = 3Hz, 1) H-2(B).
5. The same synthetic scheme was also applied in the racemic series.
6. D. ENDERS, H. EICHENAVER and D. PIETER, Chem. Ber., 1979, 112, 3703.
7. Spectral data of (±)-**13**[5]. IR (CH_2Cl_2, film) νmax : 1766 (C=O) and 1602 cm^{-1}.^1H NMR ($CDCl_3$) δ(ppm) : 7.35 (m, 10) aryl H ; 7.10-6.35 (m, 6) aryl H ; 6.20 (wide s, 1) OH ; 5.12 (s, 2) $ArOC\underline{H}_2$ - ; 4.6-3.6 (m, 5) CH_2O and >CH-O- ; 3.75 (s, 6) OCH_3 ; 2.8-2.3 (m, 4).
8. Spectral data of (±)-**14**.[5] IR (CH_2Cl_2, film) νmax : 1766 (C=O) and 1608 cm^{-1}. ^1H NMR ($CDCl_3$)δ (ppm) : 7.40 (m, 5) aryl H ; 7.1-6.40 (m, 6) aryl H ; 5.7 (wide s,2) OH ; 4.7-4.0 (m, 5) CH_2O and >CH-O- ; 3.81 (s, 3) OCH_3 ; 3.75 (s, 3) OCH_3 ; 2.9-2.3 (m, 4).
9. K. FREUDENBERG and L. KNOF, Chem. Ber., 1957, 90, 2957.
10. Spectral data of the O-diacetyl derivative of (-)-α-conidendrin **2**. IR (CH_2Cl_2, film) νmax : 1766 (wide, C=O) and 1602 cm^{-1}. ^1H NMR ($CDCl_3$) δ(ppm) : 7.1 (d, J = 8Hz, 1) H-5' ; 6.86 (s,1) H-8 ; 6.80 (dd, 1) H-6' ; 6.73 (1) H-2' ; 6.60 (s, 1) H-5 ; 4.4-3.7 (3) CH_2O and H-4 ; 3.85 (s, 3) OCH_3 ; 3.77 (s, 3) OCH_3 ; 3.5-2.9 (m, 2) CH_2-9 ; 2.9-2.4 (m, 2) H-3a and H-9a ; 2.30 (s, 3) CH_3CO ; 2.21 (s, 3) CH_3CO.
11. a) R.C. CAMBIE, G.T.M. PANG, J.C. PARNELL, R. RODRIGO and R.J. WESTON, Aust. J. Chem., 1979, 32, 2741 ; b) R.C. CAMBIE, G.R. CLARK, P.A. CRAW, T.C. JONES, P.S. RUTLEDGE and P.D. WOODGATE, Aust. J. Chem., 1985, 38, 1631.

(Received in France 20 June 1989)