following solutions were prepared for enzymatic assay: (1) PIPES–NaOAc buffer (0.01 M PIPES, 0.2 M NaOAc and 0.01 mM EDTA, pH 6.5). This buffer was prepared according to the literature procedure.[19] (2) α-D-Glucosidase: 1.5 mg of solid protein (70 U/mg) was dissolved in 1 mL of PIPES–NaOAc buffer solution and used for assay without dilution. (3) β-D-Glucosidase: the assay enzyme solution was prepared by dissolving 20 mg of solid protein (4.8 U/mg solid) in 6 mL of PIPES–NaOAc buffer solution. (4) α-D-Mannosidase: 5 mg of solid protein was suspended in 1 mL of 3 M $(NH_4)_2SO_4$ and 0.1 M ZnOAc. (5) α-D-Galactosidase: 5 U of α-galactosidase was dissolved in 2.2 mL of PIPES–NaOAc buffer solution. (6) β-D-Galactosidase: 0.5 mg of solid protein (345 U/mg) was dissolved in 1 mL of PIPES–NaOAc buffer solution.

General Procedure for Enzyme Assay. For each inhibitor, four or five inhibitor concentrations, ranging from 0 to 3 times K_i, were used to determine the K_i value. At each inhibitor concentration, five substrate concentrations were used to obtain a single Lineweaver–Burk plot (Figure 5). The amount of enzyme added in each assay was adjusted so that less than 10% of the substrate, with its lowest substrate concentration, would be consumed within 1 min. The assays were monitored at 400 nm for measuring the released *p*-nitrophenol group. The following example illustrates the procedure in detail.

To a 1-mL disposable cuvette was added 950 μL of NaOAc–PIPES buffer solution, 20 μL of inhibitor solution, and 20 μL of *p*-nitrophenol α-D-glucoside solution (25 mM in PIPES–NaOAc buffer, pH 6.5). The solution was well mixed and 20 μL of α-D-glucosidase solution was added to the cuvette to start the reaction. The reaction was monitored at 400 nm on a Beckman DU-70 spectrophotometer for 1 min and the initial hydrolysis rate was calculated. The same procedure was repeated with four other substrate concentrations. After all the initial rates were obtained, the corresponding Lineweaver–Burk plot at that inhibitor concentration was constructed.

(19) Dale, M. P.; Ensley, H. E.; Kern, K.; Sastry, K. A. R.; Byers, L. D. *Biochemistry* **1985**, *24*, 3530.

Acknowledgment. We thank Drs. A. B. Reitz and Bruce Maryanoff at the R. W. Johnson pharmaceutical Research Institute for valuable suggestions and discussion.

Supplementary Material Available: NMR spectra (^1H or ^{13}C) of **4a**, **4b**, **5a**, **5b**, **7**, **8**, **10**, **11**, and **17** (9 pages). Ordering information is given on any current masthead page.

C-Glycosides. 9. Stereospecific Synthesis of *C*-Glycosidic Spiroketal of the Papulacandins

Stanislas Czernecki* and Marie-Claude Perlat

Laboratoire de Chimie des Glucides, Université Pierre et Marie Curie, T 74, E6, 4, place Jussieu, 75005 Paris, France

Received December 11, 1990

The reaction of ortho-lithiated triphenylmethyl benzyl ether with perbenzylated D-gluconolactone 1 followed by cyclization by $BF_3{\cdot}Et_2O$ provides a new stereospecific synthesis of *C*-glycosidic spiroketals. The structure of the peracetylated derivative was determined by X-ray diffraction. This methodology is applied to the synthesis of the spiroketal unit of papulacandins.

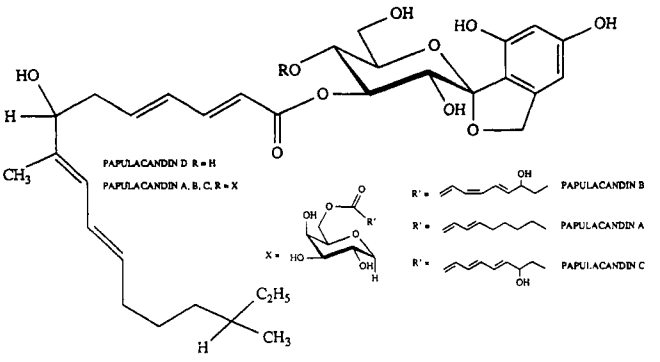
The papulacandins (A–D) are antifungal antibiotics that were isolated from a strain of *Papularia sphaerosperma*.[1] These four papulacandins are built on the same skeleton and differ only by substitution of one hydroxyl of papulacandin D by different groups (Chart I).

From a synthetic standpoint, the most interesting feature in these molecules represents the spiroketal unit involving a substituted aromatic ring β C–C linked to a glucopyranosyl moiety. Different approaches toward the synthesis of the spiroketal of papulacandin have been reported: lengthy partial synthesis of the racemic form[2] and multistep synthesis of the pure enantiomer from D-glucose.[3]

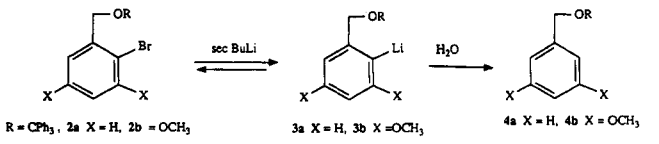
As a part of a continuing program of C–C bond formation at the anomeric center of a sugar moiety, we have initiated some studies in that area and preliminary results were published.[4]

In a previous work,[5] we demonstrated that aryl-β-D-*C*-glucosides could be prepared in a stereospecific manner by condensation of an aryllithium derivative with 2,3,4,6-tetra-*O*-benzyl-D-gluconolactone[6] (1) followed by reduction by triethylsilane in the presence of $BF_3{\cdot}Et_2O$. We also observed that, under these conditons, a 1,5-anhydro derivative was obtained from protected ribonolactone, indicating the participation of O-5 and the cleavage of *O*-trityl and *O*-silyl ethers.[7] So, we anticipated

Chart I



Scheme I



(1) Traxler, P.; Gruner, J.; Anden, J. A. L. *Antibiotics* **1977**, *30*, 289.
(2) Danishefsky, S.; Phillips, G.; Ciufolini, M. *Carbohydr. Res.* **1987**, *171*, 317.
(3) Schmidt, R. R.; Frick, W. *Tetrahedron* **1988**, *44*, 7163.
(4) Czernecki, S.; Perlat, M-C. *J. Carbohydr. Chem.* **1990**, *9*,(6), 915.
(5) Czernecki, S.; Ville, G. *J. Org. Chem.* **1989**, *54*, 610.
(6) Kuzuhara, H.; Fletcher, J. G., Jr. *J. Org. Chem.* **1967**, *32*, 2531.

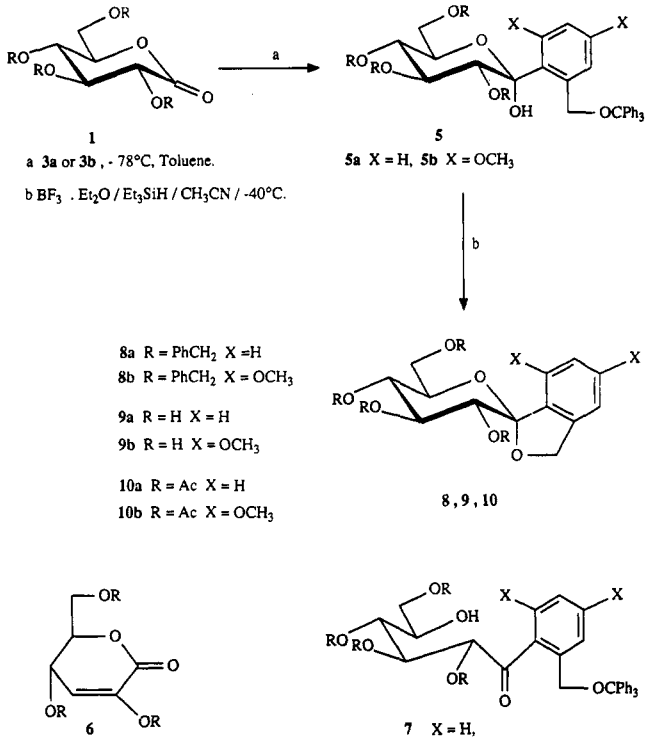
0022-3263/91/1956-6289$02.50/0

Table I. Preparation of the Aryllithium Derivative

entry	X	solvent	θ (deg)	time (min)	2[a] (%)	4[a] (%)
1	H	THF	25	5	45	55
2	H	THF	-78	15	40	60
3	H	pet. ether	25	60		100
4	H	pet. ether	-78	60	100	
5	H	toluene	25	5	3	97
6	H	toluene	-78	15	3	97
7	OCH_3	toluene	25	15	10	62[b]
8	OCH_3	toluene	-78	15	5	97

[a] Determined after hydrolysis and separation of **2a,b** and **4a,b** by preparative TLC. [b] Other unidentified compounds were also formed.

Scheme II



that the product resulting from condensation of 1 with an organolithium derivative bearing a suitably placed *O*-trityl ether could directly cyclize during the reduction step. Based on previous results,[5] the correct configuration was expected at the anomeric center.

Although the reaction of 1 with diversely alkoxylated aryllithium derivatives was reported not to give encouraging results,[2,3,8] the organolithium derivative **3a** was chosen as a model compound to study the feasibility of our approach.[9] It was prepared by metal–halogen exchange between triphenylmethyl 2-bromobenzyl ether (**2a**) and *sec*-butyllithium (Scheme I).

Although the exchange was not complete in this solvent (Table I, entries 1 and 2), THF was employed for preliminary studies. An addition of **3a** (1.4 equiv) to a cooled solution (-78 °C) of 1 afforded, after hydrolysis, a mixture of hemiketals **5a** (19% yield), but the major product was the unsaturated lactone **6**.[10] This competitive elimination

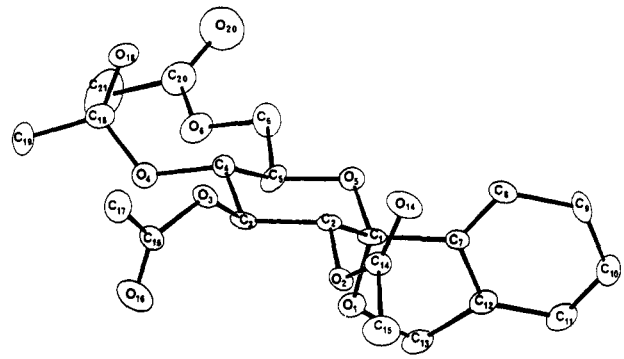


Figure 1.

due to the basic character of the aryllithium derivative in THF was also observed by others,[9a] who isolated **6** (50%) together with a mixture of anomeric spiroketals (28%). Other less polar solvents were evaluated (see Table I) in which formation of an ion pair was expected to decrease the basicity of the aryllithium derivative. Toluene was chosen because the high solubility of **1** in this solvent ensured a homogeneous solution even at low temperature.

Transfer of the soobtained solution of **3a** (1.4 equiv) to a solution of 1 in toluene at -78 °C gave after hydrolysis with a saturated aqueous solution of ammonium chloride **5a** together with triphenylmethyl benzyl ether. By analogy with D-*gluco*-heptulose, which is practically only in the α-pyranose form,[11] the structure **5a** could be attributed to the hemiketal. No spiroketals or unsaturated lactone **6** were detected in the reaction mixture, but when water alone was employed for hydrolysis, the open-chain ketone **7** was observed, which was in agreement with previous results.[9a] Crude **5a** was treated with BF_3·Et_2O and triethylsilane in acetonitrile at -40 °C. After workup and purification, crystalline perbenzylated spiroketal **8a** was obtained from 1 in 61% overall yield. Actually, the reducing agent (Et_3SiH) is not necessary and the cyclization could be achieved with BF_3·Et_2O alone, but in this case the yield is lower (40%). In the presence of Et_3SiH the cyclic intermediate formed by participation of the benzylic oxygen was rapidly reduced into the spiroketal **8a** and triphenylmethane as shown by TLC. Thus, side reactions were avoided and the reaction was cleaner: only two spots were detected by TLC and the spiroketal was isolated in 74% yield from **5a**. It has been found that triethylsilane could be added before or after BF_3·Et_2O without affecting the yield (56 and 61%, respectively, from 1). In all cases, only one stereoisomer was obtained. The β configuration of the C–C bond at the anomeric center of **8a** was confirmed by ^{13}C NMR[12a,b] and comparison of chemical shift of C-1 with other known *C*-glycosides.[12c]

Debenzylation of **8a** in a mixture of solvents (methanol–ethyl acetate (1:1)) afforded **9a** in quantitative yield. Under these conditions, none of the three other O-benzylic bonds present in the spiroketal rings was cleaved.

Additional structural proofs were obtained from the peracetylated derivative **10a**. The presence of only four acetoxy groups in **10a**, as determined by ^1H NMR (4s, δ 1.72, 2.0, 2.05, 2.07), confirmed that the spiroketal function was not affected during the debenzylation step. Furthermore, the large values of the coupling constants be-

(7) The participation of $OSiR_3$ and of OTr groups in forming ethers (glycosides) from oxonium ions has already been observed: (a) Bredereck, H.; Wagner, A.; Faber, G.; Ott, H.; Rauther, J. *Chem. Ber.* **1959**, *92*, 1135. (b) Klemer, A.; Gaupp, K.; Buhe, E. *Tetrahedron Lett.* **1969**, *52*, 4585.

(8) Kraus, G. A.; Molina, M. T. *J. Org. Chem.* **1988**, *53*, 752.

(9) While this paper was in preparation, two other approaches for the synthesis of papulacandin appeared: (a) Rosenblum, S. B.; Bihovsky, R. *J. Am. Chem. Soc.* **1990**, *112*, 2746. (b) Dubois, E.; Beau, J. M. *Tetrahedron Lett.* **1990**, *36*, 5165.

(10) Hall, R. H.; Bischofberger, K.; Eitelman, S. J.; Jordaan, A. *J. Chem. Soc., Perkin Trans, 1* **1977**, 2236.

(11) Angyal, S. J.; Tran, T. Q. *Aust. J. Chem.* **1983**, *36*, 937.

(12) (a) Bock, K.; Pedersen, C. *Adv in Carbohydr. Chem. Biochem.* **1983**, *41*, 26. (b) Agrawal, P. K.; Jain, D. C.; Gupta, R. K.; Thakur, R. S. *Phytochem.* **1985**, *11*, 2479. (c) Bellosta, V.; Chassagnard, C.; Czernecki, S. *Carbohydr. Res.*, in press.

tween $H_{2'}$, $H_{3'}$, $H_{4'}$, and $H_{5'}$ (10 Hz) were in agreement with previous reports[2,3] and clearly indicated a $^4C_1$ D conformation for the pyranoside ring. This observation is a good indication for the equatorial (β) orientation of the aromatic ring because in the α-anomer of phenyl-D-C-glucopyranoside the coupling constants are smaller due to conformational changes.[12c,13]

Finally, crystals of **10a** suitable for X-ray diffraction were obtained. The crystallographic structure (ORTEP) and atomic numbering are shown in Figure 1.

Since the sugar moiety is known to be a D-glucopyranose, X-ray data unambiguously established the α configuration of C(1). The observed bond lengths and angles in **10a** are in good agreement with those already determined in naturally occurring papulacandins A, B, and C.[14]

When the same sequence of reactions was applied to **1** with aryllithium derivative **3b**, the protected spiroketal unit of papulacandin **8b** was obtained in similar yield (57%).

Debenzylation to **8b** was possible without any ring cleavage, and **10b** was obtained by acetylation and used for structural determination. The ^1H NMR data were in agreement with those previously reported[2,3] and clearly indicated the same configuration at the anomeric center for **10a**.

This cyclization of strategically functionalized hemiketals constitutes a very straightforward synthesis of C-glycosidic spiroketals. The efficiency of this methodology is herein exemplified by the synthesis of papulacandin spiroketal unit.

Experimental Section

General Methods. Optical rotations were measured on a Perkin-Elmer 141 polarimeter. IR spectra (film, KBr disk) were recorded on a Unicam SP3-300 spectrophotometer. ^1H NMR and ^{13}C NMR spectra were recorded in $CDCl_3$ or C_6D_6, using Me_4Si as an internal standard, with a Brucker AM-250 apparatus operating in the FT mode at 250 or 63 MHz, respectively. Analytical TLC was performed on precoated aluminum plates (E. Merck silica gel $60F_{254}$). For flash chromatography, E. Merck silicagel 60 (230–400 mesh) and anhydrous solvents were used. Mass spectra (MS) were obtained on a Nermag R 10-10 spectrometer using chemical ionization (NH_3).

Triphenylmethyl 2-Bromobenzyl Ether (2a). Triphenylmethyl chloride (1.02 g, 3.66 mmol) was added to a solution of 2-bromobenzyl alcohol in pyridine (15 mL) at 100 °C. The solution was heated at 100 °C for 7 h. The reaction mixture was poured into water (150 mL), and the precipitate was filtered off affording **2a** (1.218 g, 95% yield). Recrystallization from ethanol gave pure **2a** (0.834 g, 65% yield): mp 138–139 °C. Anal. Calcd for $C_{26}H_{21}BrO$: C, 72.72; H, 4.93. Found: C, 72.26, H, 4.91.

Triphenylmethyl 2-Bromo-3,5-dimethoxybenzyl Ether (2b). This compound was prepared from 2-bromo-3,5-dimethoxybenzyl alcohol[15] (1.59 g, 6.42 mmol) (2.41 g, 77% yield) as described above. Recrystallization from ethanol afforded pure **2b** (1.15 g): mp 137–138 °C. Anal. Calcd for $C_{28}H_{25}BrO_3$: C, 68.71; H, 5.11. Found: C, 68.26; H, 5.09.

General Procedure for the Preparation of Aryllithium Derivatives 3a and 3b. The desired aryllithium derivatives **3a** and **3b** were prepared by halogen–metal exchange.[16] *sec*-Butyllithium (1.4 M, 1 mmol) was added dropwise to aryl bromide **2a** or **2b** (1 mmol) in the chosen solvent (3 mL). After 15 min of stirring, the mixture was quenched with a saturated aqueous solution of NH_4Cl (1 mL) and extracted three times with ethyl acetate (10 mL). The organic layers were dried over magnesium sulfate and concentrated in vacuo. The aryl bromides **2a** or **2b** were separated from aryl products **4a** or **4b** by preparative TLC with petroleum ether–methylene chloride (8:2) for **2a** (R_f 0.60) and **4a** (R_f 0.57); petroleum ether–methylene chloride (6:4) for **2b** (R_f 0.49) and **4b** (R_f 0.46). These tries were performed in different solvents, at different temperatures and different times (see Table I).

1,1-Anhydro-1-C-[2-(hydroxymethyl)phenyl]-2,3,4,6-tetra-O-benzyl-β-D-glucopyranose (8a). *sec*-Butyllithium (1.4 M, 0.53 mL, 0.74 mmol, 142 mol %) was added dropwise to aryl bromide **2a** (316 mg, 0.74 mmol, 142 mol %) in toluene (3 mL) at room temperature. After 15 min of stirring, the mixture was transferred under a pressure of argon to the cooled solution (−78 °C) of gluconolactone **1** (283 mg, 0.53 mmol) in toluene (3 mL). After 15 min at −78 °C, the reaction was quenched with a saturated aqueous solution of ammonium chloride (1 mL). The temperature was then allowed to rise to room temperature, and the mixture was stirred for another 30 min. The mixture was then extracted with ethyl acetate (3 × 20 mL), and the organic layer, after being dried over anhydrous magnesium sulfate, was evaporated under reduced pressure, affording crude **5a** as a colorless oil (470 mg). The crude product (470 mg) was dissolved in acetonitrile (5 mL), the solution was cooled to −40 °C and then $BF_3{\cdot}Et_2O$ (73 μL, 0.583 mmol) and triethylsilane (86 μL, 0.583 mmol) were successively added. After 15 min, the reaction was quenched with a saturated aqueous solution of potassium carbonate (1 mL). The aqueous layer was extracted with ethyl acetate (3 × 20 mL), and the organic layer was dried over anhydrous magnesium sulfate and the solvent evaporated under reduced pressure. Chromatography of the crude product with petroleum ether as eluent afforded pure **8a** (205 mg, 62% yield): R_f 0.47 with ether–petroleum ether (1:1); $[\alpha]_D$ = +23.6° (*c* 1.6, $HCCl_3$); MS *m/z* 629 (M + 1), 646 (M + NH_4^+); ^1H NMR (C_6D_6) δ 7.37–6.77 (m, 24, H arom), 5.03 (br, 2, ArCH_2O–), 5.07–4.13 (m, 8, ArCH_2O–), 4.57 (d, 1 $J_{2',3'}$ = 10.6 Hz, H2′), 4.43 (dd, 1, H4′), 4.04 (dd, 1, $J_{3',2'}$ = 10.6 Hz, H3′), 3.86 (m, 2, H6′, H6″), 3.66 (ddd, 1, $J_{5',4'}$ = 10.6 Hz, $J_{5',6'}$ = 3.2 Hz, H5′); ^{13}C NMR ($CDCl_3$) 140.56, 138.82, 138.42, 138.3, 129.31, 128.35, 128.30, 128.04, 127.90, 127.79, 127.75, 127.68, 127.64, 127.57, 127.48, 127.44, 122.25, 120.93 (C, arom), 109.98 (C1′), 83.78 (C3′), 82.76 (C5′), 78.17 (C2′), 75.66, 75.17, 74.88, 73.30, 73.05 (ArCH_2O–), 73.23, (C4′), 68.82 (C6′). Anal. Calcd for $C_{41}H_{40}O_6$: C, 78.34; H, 6.42. Found: C, 77.92; H, 6.66.

1,1-Anhydro-1-C-[2-(hydroxymethyl)phenyl]-β-D-glucopyranose (9a). A solution of **8a** (251 mg) in methanol (1 mL) and ethyl acetate (1 mL) was hydrogenated at atmospheric pressure over 10% palladium on charcoal (30 mg) for 5 h at room temperature. The catalyst was filtered off using Celite (500 mg), and the solids were washed with methanol. Evaporation of the filtrate afforded pure **9a** (171 mg, 98%): R_f 0.47 with dichloromethane–methanol (80:20); mp 62 °C, $[\alpha]_D$ = +38.8° (*c* 1, $CHCl_3$); MS *m/z* 269 (M + 1), 286 (M + NH_4^+). Anal. Calcd for $C_{13}H_{16}O_6$: C, 58.26; H, 5.97. Found: C, 57.83; H, 6.30.

1,1-Anhydro-1-C-[2-(hydroxymethyl)phenyl]-2,3,4,6-tetra-O-acetyl-β-D-glucopyranose (10a). The compound **9a** (120 mg) was treated with acetic anhydride (190 μL), pyridine (1 mL), and DMAP (1 crystal) at room temperature. After 48 h, pyridine was evaporated and ice–water (5 mL) was added. The mixture was extracted with ethyl acetate (3 × 20 mL), and the organic layer was washed with 5% hydrochloric acid (10 mL) and then 5% aqueous solution of sodium hydroxide (10 mL). The organic layer was dried over anhydrous magnesium sulfate, concentrated in vacuo, and then purified by preparative TLC, yielding **10a** (74 mg, 90%): R_f 0.43 with ether–petroleum ether (50:25); mp 112–113 °C (ether–isopropyl ether); $[\alpha]_D$ = +23.5° (*c* 1.1, $CHCl_3$); ^1H NMR (C_6D_6) δ 6.70–7.59 (m, 4, H arom), 6 (t, 1, $J_{3',2'}$ = $J_{3',4'}$ = 9.8 Hz, H3′), 5.84 (d, 1, $J_{2',3'}$ = 10 Hz, H2′), 5.54 (t, 1, $J_{4',5'}$ = $J_{4',3'}$ = 9.8 Hz, H4′), 4.84 (s, 2, ArCH_2O–), 4.38 (dd, 1 $J_{6',6''}$ = 13.2 Hz, $J_{5',6''}$ = 7.4 Hz, H6′), 4.32 (m, 1, $J_{5',6'}$ = 6.2 Hz, $J_{5',6''}$ = 2.5 Hz, H5′), 4.01 (dd, 1, $J_{6',6''}$ = 13 Hz, $J_{6'',5'}$ = 2.5 Hz, H6″, 1.74 (s, 3, CH_3CO–), 1.72 (s, 3, CH_3CO–), 1.65 (s, 3, CH_3CO–), 1.34 (s, 3, CH_3CO–). Anal. Calcd for $C_{21}H_{24}O_{10}$: C, 57.85; H, 5.55. Found: C, 57.98; H, 5.53.

1,1-Anhydro-1-C-[2-(hydroxymethyl)-4,6-dimethoxyphenyl]-2,3,4,6-tetra-O-benzyl-β-D-glucopyranose (8b). Condensation of aryllithium **3b**, obtained by exchange [*sec*-butyllithium (1.4 M, 1.2 mL, 1.66 mmol, 250 mol %) and aryl bromide **2b** (813 mg, 1.66 mmol, 250 mol %) at −78 °C] with **1**

(13) Bellosta, V. Ph. D. Thesis, Université Pierre et Marie Curie, Paris, 1987.
(14) Rihs, G.; Traxler, P. *Helv. Chim. Acta* **1981**, *64*, 1533.
(15) Noire, P. D.; Franck, R. W. *Synthesis* **1980**, 882.
(16) Tropka, W. J.; Sonnenfeld, R. J. *J. Organomet. Chem.* **1969**, *16*, 317.

(357 mg, 0.67 mmol) in toluene (20 mL) afforded **8b** (257 mg, 57%): R_f 0.32 with ether-petroleum ether (1:1); mp 63-64 °C (methanol-ethyl acetate); $[\alpha]_D$ = +8.3° (*c* 1.4, $CHCl_3$); ^{13}C NMR ($CDCl_3$) 143.83, 138.84, 138.72, 138.53, 138.43, 130.81, 128.73, 128.29, 128.24, 128.09, 127.92, 127.85, 127.73, 127.44, 127.2 (C arom), 109.94 (C1'), 98.11 and 96.75 (OCH_3) 83.67 (C3'), 81.03 (C5'), 78.24 (C2'), 75.66, 74.84, 74.58, 73.08, 72.98 (-CH_2Ar), 73.29 (C4'), 68.76 (C6'). Anal. Calcd for $C_{43}H_{44}O_8$: C, 75.06; H, 6.45. Found: C, 74.49; H, 6.48.

1,1-Anhydro-1-*C*-[2-(hydroxymethyl)-4,6-dimethoxyphenyl]-β-D-glucopyranose (9b). Hydrogenolysis of **8b** (165 mg, 0.24 mmol) in methanol (1 mL) and ethyl acetate (1 mL) in the presence of 10% palladium on charcoal (20 mg) afforded **9b** in quantitative yield (83 mg), which was purified by preparative TLC (68 mg, 87%): R_f 0.40 with dichloromethane-methanol (80:20); mp 97-98 °C (ethyl acetate); $[\alpha]_D$ = +48.1° (*c* 0.43, $CHCl_3$); MS *m/z* 329 (M + 1). Anal. Calcd for $C_{15}H_{20}O_8$: C, 54.92; H, 6.15. Found: C, 54.89; H, 6.27.

1,1-Anhydro-1-*C*-[2-(hydroxymethyl)-4,6-dimethoxyphenyl]-β-D-glucopyranose Tetraacetate (10b).[2,3] Acetylation of **9b** (44 mg, 0.128 mmol) according to the procedure described for the preparation of **10a** [acetic anhydride (128 μL), pyridine (1 mL), and DMAP (1 crystal)] afforded **10b**, which was purified by preparative TLC (47 mg, 74%): R_f 0.41 with petroleum ether-ethyl acetate (1:1); mp 159-160 °C (petroleum ether) (lit.[3] mp 70-72 °C); $[\alpha]_D$ = +7° (*c* 1, $CHCl_3$) [lit.[3] $[\alpha]_D$ = +5° (*c* 1, $CHCl_3$)]; MS *m/z* 496 (M + 1); ^1H NMR ($CDCl_3$) δ 6.30-6.28 (2s, 2, H arom), 5.89 (d, 1, $J_{2',3'}$ = 9.98 Hz, H2'), 5.55 (t, 1, $J_{3',2'} = J_{3',4'}$ = 9.84 Hz, H3'), 5.30 (t, 1, $J_{4',3'} = J_{4',5'}$ = 9.9 Hz, H4'), 5.16 (d, 1, *J* = 12.7 Hz, ArCH_2O-), 5.03 (d, 1, *J* = 12.7 Hz, ArCH_2O-), 4.28-4.07 (2 m, 3, H5', H6', H6''), 3.82 (s, 3, -OCH_3), 3.78 (s, 3, CH_3CO-), 1.99 (s, 3, CH_3CO-), 1.73 (s, 3, CH_3CO-). Anal. Calcd for $C_{23}H_{28}O_{12}$: C, 55.69; H, 5.69. Found: C, 55.70; H, 5.74.

Acknowledgment. Dr. J. M. Valéry is acknowledged for recording the ^{13}C and ^1H NMR spectra and Dr. J. Vaissermanne (Laboratoire de Chimie des Métaux de Transition) for the structure determination of **10a** by X-ray diffraction.

Registry No. 1, 13096-62-3; **2a**, 132814-55-2; **2b**, 135877-95-1; **3a**, 135877-99-5; **3b**, 135878-00-1; **4a**, 5333-62-0; **4b**, 135877-96-2; **5a**, 132814-51-8; **5b**, 135877-97-3; **6**, 62641-00-3; **8a**, 132814-52-9; **8b**, 135877-98-4; **9a**, 132814-53-0; **9b**, 76843-39-5; **10a**, 132814-54-1; **10b**, 76843-40-8; 2-$BrC_6H_4CH_2OH$, 18982-54-2; 2-Br-3,5-$(MeO)_2C_6H_2CH_2OH$, 74726-76-4; papulacandin A, 61036-46-2; papulacandin B, 61032-80-2; papulacandin C, 61036-48-4; papulacandin D, 61036-49-5.

Supplementary Material Available: Crystallographic data for compound **10a** (6 pages). Ordering information is given on any current masthead page.

Synthetic Applications of Protected 2-Aryl-4-piperidones. 7.[1] Synthesis of 1-Ethylindolo[2,3-*a*]quinolizidin-2-one[§]

Mario Rubiralta,*[†] Anna Diez,[†] Cristina Vila,[†] Yves Troin,[†] and Miguel Feliz[‡]

Laboratory of Organic Chemistry, Faculty of Pharmacy, University of Barcelona, 08028 Barcelona, Spain, and Department of Organic Chemistry, Faculty of Chemistry, University of Barcelona, 08028 Barcelona, Spain

Received April 12, 1991

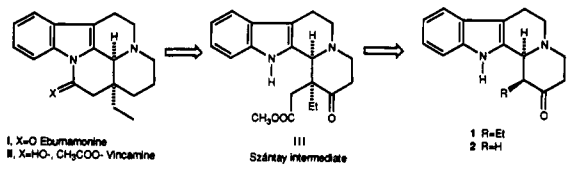
The synthesis of 1-ethylindolo[2,3-*a*]quinolizidin-2-one (1) by the intramolecular cyclization of protected *N*-(2-hydroxyethyl)-2-[1-(phenylsulfonyl)-3-indolyl]-4-piperidone **15** by the action of K^{t}BuO and further acid treatment is reported. The methodology has been first carried out for its deethyl analogue **2** from (hydroxyethyl)piperidine **14** and has shown to be a good general method to reach indolo[2,3-*a*]quinolizidin-2-one systems. Compound **1** has also been obtained by an unusual rearrangement in acidic medium of 7-ethylhexahydropyrido[1',2':1,2]pyrazino[4,3-*a*]indole.

Introduction

In continuing our studies of the synthesis of the indolo[2,3-*a*]quinolizidin-2-one system[2] as a new synthetic application of easily accessible protected 2-aryl-4-piperidones,[3] we report now the synthesis of 1-ethylindolo[2,3-*a*]quinolizidin-2-one (**1**), which can be considered a key intermediate in the preparation of pentacyclic indole alkaloids of the vincamine type,[4] some of which, such as (-)-eburnamonine and (+)-vincamine,[5] are used in medicine for their vasodilator properties (Scheme I).

In previous work, we already reported the synthesis of the indolo[2,3-*a*]quinolizidin-2-one basic framework (**2**),[2b] as well as its 3-ethyl derivative,[2a] by the intramolecular cyclization of protected *N*-(2-hydroxyethyl)-2-[1-(phenylsulfonyl)-2-indolyl]-4-piperidones (**3** and **4**) by the initial action of potassium *tert*-butoxide.[6] However, the cyclization occurred as well, to some extent, upon the indole nitrogen atom, yielding the corresponding hexahydro-4*H*-

Scheme I



[†] Faculty of Pharmacy.

[‡] Faculty of Chemistry.

[§] This work is dedicated to Professor Fèlix Serratosa for his long and impressive years of research.

(1) For part VI, see: Rubiralta, M.; Marco, P.; Bolós, J.; Trapé, J. *Tetrahedron* **1991**, *47*, 5585-5602.

(2) (a) Rubiralta, M.; Diez, A.; Bosch, J.; Solans, X. *J. Org. Chem.* **1989**, *54*, 5591-5597. (b) Rubiralta, M.; Diez, A.; Vila, C. *Tetrahedron* **1990**, *46*, 4443-4456. (c) Rubiralta, M.; Diez, A.; Vila, C. *Tetrahedron Lett.* **1990**, *31*, 3347-3350. (d) Rubiralta, M.; Diez, A.; Vila, C. *Tetrahedron Lett.* **1990**, *31*, 3779-3782.

(3) (a) Bosch, J.; Rubiralta, M.; Moral, M.; Bolós, J. *J. Chem. Soc., Perkin Trans. 1* **1984**, 1459-1464. (b) Bosch, J.; Rubiralta, M.; Moral, M.; Ariño, J. *J. Chem. Soc., Perkin Trans. 1* **1986**, 1533-1539. (c) Rubiralta, M.; Diez, A.; Balet, A.; Bosch, J. *Tetrahedron* **1987**, *43*, 3021-3030. (d) Diez, A.; Tona, M.; Rubiralta, M. *Tetrahedron* **1990**, *46*, 4393-4406.

0022-3263/91/1956-6292$02.50/0