INTRAMOLECULAR *N*-ACYLIMINIUM ION-OLEFIN CYCLIZATION IN THE SYNTHESIS OF OPTICALLY PURE ISOQUINOLINE DERIVATIVES: CONTROL OF STEREOCHEMISTRY AND APPLICATION TO SYNTHESIS OF MORPHINE ALKALOIDS

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Dedicated to the memory of Dr Miroslav Protiva in recognition of his life-long contributions to the chemistry of alkaloids.

The 3-[2-(cyclohex-1-enyl)ethyl]-[1,3]oxazoline-2,4-dione derivatives **9**, **14** and **16** were subjected to hydride reduction followed by acid-catalyzed olefin-*N*-acyliminium ion cyclization to afford a series of perhydroisoquinolines **10**, **11a**, **11b**, **19a**–**19c**, **20a**, **20b** and **21**. A mechanism was proposed that accounts for the observed stereoselectivity of the cyclization reactions based on the neighboring group participation by a benzoate group.

Key words: *N*-Acyliminium ion; Isoquinolines; Stereochemistry; Morphine; Alkaloids; Biooxidation.

Morphine, the major component of opium, is a central nervous system depressant[1], finding applications in medicine as potent analgesic, hypnotic and cough-suppressant[2]. Currently, morphine is also being used as an anesthetic in open-heart surgery because of its inactive cardiac spectrum[3].

Although the medicinal use of morphine has been known for centuries and some 20 total syntheses have been published[4], an efficient preparation continues to be a challenge to the chemical community. An economical and practical synthesis competitive with the cost of extraction from opium

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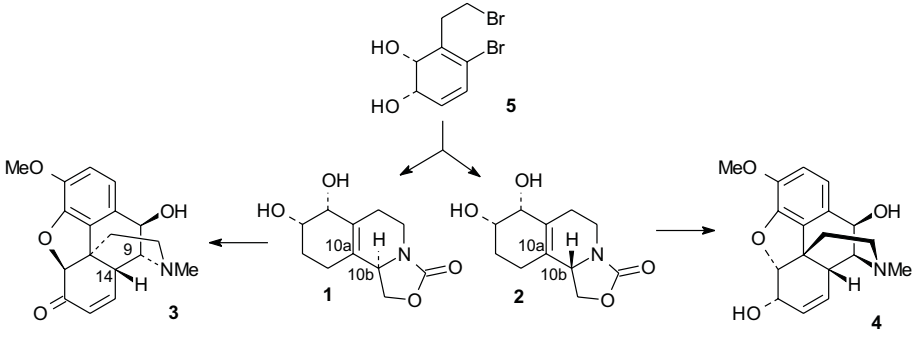
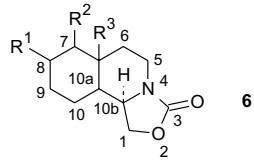
poppy and the need to synthesize simpler derivatives with varied biological activity are some of the reasons for continuing interest. As we previously reported[5], isoquinolines such as **1** and **2** seem to be ideal intermediates for the total synthesis of either enantiomer of morphine as their stereochemistry at C-10b corresponds to the absolute stereochemistry at C-9 of the *ent*-morphine **3** and the natural alkaloid **4**, respectively (Scheme 1).



SCHEME 1

One of our early attempts involved radical cyclization of a derivative of the vinyl bromide **5**, which furnished a 2 : 1 mixture of the isoquinoline derivatives **1** and **2** in 89% combined yield[5], as shown in Scheme 1. Because of the low selectivity of the radical cyclization, another route was developed[5] to control better the access to both isoquinoline isomers *via* an acid-catalyzed cyclization to furnish compounds of the type of **6**. In continuation of our efforts in this area[6], we report here the results of the study of



the stereocontrolled intramolecular *N*-acyliminium ion-olefin cyclization[7] to enantiomerically pure isoquinoline derivatives for both *cis*- and *trans*-series of protected diols **9a**, **17** and **18** synthesized from the readily available diol **7**. With this approach we were able to control the stereochemistry at C-10a/C-10b in the isoquinoline intermediates, centers that correspond to C-14/C-9 of morphine, respectively. In the *cis*-series (Scheme 2), after cyclization of the benzoate protected diol **9a**, the stereochemistry at C-10b,

which corresponds to C-9 of the natural morphine, was established in the correct absolute sense. Dehydrochlorination or dehydration reaction at C-6a/C-10a gives the isoquinoline derivative **1**, important intermediate in the natural morphine synthesis. In the *trans*-series, the adducts obtained have one of the two stereocenters C-10a or C-10b established in the correct absolute sense depending on whether the desired target is natural or *ent*-morphine. The stereochemistry at C-10a (C-14 of natural morphine) is set in the correct absolute sense and that of C-10b (C-9 of natural morphine) is reversed. Epimerization at C-10b can establish the correct stereochemistry of both stereocenters C-10a/C-10b for the natural morphine synthesis. For the *ent*-morphine approach, the analysis is opposite. The stereocenter C-10b is correct, and dehydrochlorination or dehydration reaction at C-6a/C-10a gives the isoquinoline derivative **2**, an important intermediate in the *ent*-morphine synthesis.

The outcome of the stereochemistry of the isoquinoline derivatives in the *N*-acyliminium ion cyclization reaction of the *cis*- and *trans*-series indicates that the stereochemistry at C-7 dictates the stereochemistry at C-10b and consequently at the ring junction (Fig. 1). The steric bulkiness of the benzoate group at C-7 forces the oxazolidinone ring to be near the β-face of the cyclohexene ring. Therefore, the bond formation takes place from the bottom face of the oxazolidinone ring, leading to a *cis* relationship between C-7/C-10b and a *trans* between C-10a/C-10b.

EXPERIMENTAL

All non-hydrolytic reactions were performed under an atmosphere of argon in solvents dried according standard procedures. Analytical TLC was performed on silica gel 60F-254 (Whatman) plates. Flash column chromatography was performed on Fisher silica gel (grade 60, 200–425 mesh). ^{1}H and ^{13}C NMR spectra were recorded on a Gemini 300 MHz instrument in $CDCl_3$ unless otherwise indicated. Chemical shifts are given in ppm (δ-scale), coupling constant (*J*) in Hz. All 2D NMR experiments were performed on a Varian Unity 500 MHz instru-

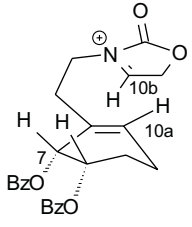


FIG. 1
Alignment for cyclization

ment. Mass spectra were recorded on a Finnigan Mat 95 Q mass spectrometer. IR spectra (wavenumbers in cm^{-1}) were obtained on a Perkin–Elmer 1600 Series instrument. X-Ray crystallography data obtained on a Siemens SMART Platform equipped with a CCD area detector. Optical rotations were measured on a Perkin–Elmer polarimeter and $[\alpha]_D$ values are given in 10^{-1} deg cm^2 g^{-1}. Elemental analyses were performed by Atlantic Microlabs, Inc. Melting points were measured on a Unimelt apparatus.

(5*S*,6*S*)-5,6-Di(benzoyloxy)-1-(2-bromoethyl)cyclohex-1-ene (**8**)

To a stirred solution of diol[8] **12** (2.0 g, 9.1 mmol), benzoic acid (2.8 g, 22.8 mmol), and catalytic amounts of DMAP in CH_2Cl_2 (80 ml) at 0 °C was added a solution of DCC (4.68 g, 22.8 mmol) in CH_2Cl_2 (10 ml). The reaction was allowed to warm up to room temperature overnight, and the solid was filtered through celite. The solvents were evaporated under reduced pressure and the residue was purified by flash chromatography on silica gel (1 : 11 ethyl acetate–hexanes) to afford the title compound as a yellow oil in 83% yield, $[\alpha]_D^{26}$ –106.7 (MeOH, *c* 0.39). ^{1}H NMR ($CDCl_3$): 2.00–2.70 (6 H, m); 3.49 (2 H, t, *J* = 7.1); 5.38 (1 H, dt, *J* = 11.2 and 3.7); 5.91 (1 H, d, *J* = 3.4); 5.94 (1 H, t, *J* = 3.9); 7.30–7.58 (6 H, m); 7.85 (2 H, d, *J* = 8.0); 8.05 (2 H, d, *J* = 8.0). ^{13}C NMR ($CDCl_3$): 22.7, 24.1, 31.0, 37.4, 68.2, 71.0, 128.2, 128.4, 129.6, 129.7, 129.9, 130.0, 130.9, 131.3, 132.8, 133.1, 165.7, 166.3. IR (neat): 2 932, 1 721, 1 601, 1 277, 1 114, 710. HRMS (CI), *m/z* for $C_{22}H_{22}BrO_4$ calculated: 429.0701; found: 429.0741.

3-{2-[(5*S*,6*S*)-5,6-Di(benzoyloxy)cyclohex-1-enyl]ethyl}-[1,3]oxazolidine-2,4-dione (**9**)

To a stirred solution of compound **8** (3.1 g, 7.2 mmol) in dry THF (60 ml) was added oxazolidinedione (0.88 g, 8.7 mmol) followed by 1,1,3,3-tetramethylguanidine (1.1 ml, 8.7 mmol). The cloudy solution was heated at reflux for 48 h and then filtered through celite. The solvents were evaporated under reduced pressure, and the residue was purified by flash chromatography on silica gel (hexanes) to furnish the title compound in 77% yield, m.p. 54–54.5 °C, $[\alpha]_D^{30}$ –124.9 (MeOH, *c* 0.43). ^{1}H NMR ($CDCl_3$): 1.2–1.4 (2 H, m); 2.00–2.50 (6 H, m); 3.74 (2 H, m); 4.66 (2 H, s); 5.37 (1 H, dt, *J* = 3.7 and 10.7); 5.82 (1 H, s); 6.00 (1 H, s); 7.29 (2 H, m); 7.45 (3 H, m); 7.57 (1 H, m); 7.85 (2 H, d, *J* = 7.1); 8.06 (2 H, d, *J* = 7.1). ^{13}C NMR ($CDCl_3$): 22.8, 24.0, 31.9, 38.5, 67.8, 68.0, 70.8, 128.2, 128.4, 129.8, 129.9, 130.1, 130.6, 130.8, 132.8, 133.1, 155.7, 165.6, 166.4, 170.3. IR (neat): 2 929, 1 815, 1 743, 1 450, 1 277. LRMS (CI), *m/z* (%): 396 (20), 264 (20), 206 (25), 178 (100). For $C_{25}H_{23}NO_7$ calculated: 66.82% C, 5.12% H, 3.12% N; found: 66.63% C, 5.51% H, 3.02% N.

(6a*R*,7*R*,8*S*,10a*R*,10b*S*)-7,8-Di(benzoyloxy)-6a-hydroxy-1,5,6,6a,7,8,10a,10b-decahydro[1,3]oxazolo[4,3-*a*]isoquinolin-3(3*H*)-one (**10**)

To a solution of compound **9** (0.80 g, 1.78 mmol) in MeOH (20 ml) at 0 °C was added $NaBH_4$ (0.68 g, 17.8 mmol) in one portion. The reaction was stirred for 30 min and quenched with acetone. The solvents were evaporated under reduced pressure and the residue extracted with ether (20 ml). The ether solution was then washed with brine (2 × 10 ml) and the solvents were evaporated under reduced pressure to afford compound **9a** (0.67 g) in 80% crude yield. Compound **9a** was used as crude material in the next step.

To a solution of **9a** (0.67 g, 1.48 mmol) in dry CH_2Cl_2 (20 ml) under argon at 0 °C was added $BF_3{\cdot}Et_2O$ (1.92 ml, 14.8 mmol) dropwise. The reaction mixture was stirred at 0 °C for

1 h, and then allowed to warm up to room temperature overnight. The reaction was quenched with saturated $NaHCO_3$ solution (10 ml), washed with brine, and dried over anhydrous Na_2SO_4. The organic solvents were evaporated under reduced pressure and the residue was purified by flash chromatography on silica gel (1 : 1 hexanes–ethyl acetate) to afford the title compound in 55% yield, m.p. 87.5–88 °C, $[\alpha]_D^{26}$ +110.4 (MeOH, *c* 1.0). ^{1}H NMR (500 MHz, $CDCl_3$): 1.39 (1 H, d, *J* = 14.9); 1.51 (1 H, td, *J* = 5.5 and 13.6); 1.91 (1 H, d, *J* = 15.0); 1.92 (1 H, t, *J* = 15.4); 1.95 (1 H, d, *J* = 12.8); 2.11 (1 H, dq, *J* = 2.9 and 15.6); 2.43 (1 H, tt, *J* = 4.5 and 14.9); 3.07 (1 H, td, *J* = 2.9 and 13.7); 3.60 (OH, s); 3.84 (1 H, ddd, *J* = 1.5, 5.7 and 14.3); 3.91 (1 H, ddd, *J* = 5.3, 8.1 and 12.3); 4.01 (1 H, dd, *J* = 5.2 and 8.7); 4.45 (1 H, t, *J* = 8.4); 5.52 (1 H, d, *J* = 3.6); 5.77 (1 H, q, *J* = 3.0); 7.35 (2 H, t, *J* = 7.5); 7.47 (2 H, t, *J* = 7.5); 7.53 (1 H, t, *J* = 7.3); 7.60 (1 H, t, *J* = 7.9); 7.93 (2 H, d, *J* = 7.9); 8.01 (2 H, d, *J* = 7.9). ^{13}C NMR (125 MHz, $CDCl_3$): 15.9, 24.2, 32.9, 37.7, 46.7, 52.9, 66.7, 67.9, 70.7, 72.2, 128.3, 128.9, 129.3, 133.5, 133.9, 156.7, 165.2, 165.8. IR ($CHCl_3$): 3 467, 2 954, 1 720, 1 276, 1 115. HRMS (EI), *m/z* for $C_{25}H_{25}NO_7$ calculated: 451.1631; found: 451.1582. For $C_{25}H_{25}NO_7$ calculated: 66.52% C, 5.54% H, 3.10% N; found: 66.56% C, 5.79% H, 3.07% N.

(6a*R*,7*S*,8*S*,10a*R*,10b*S*)-7,8-Di(benzoyloxy)-6a-chloro-1,5,6,6a,7,8,9,10,10a,10b-decahydro[1,3]oxazolo[4,3-*a*]isoquinolin-3(3*H*)-one (**11a**) and (6a*S*,7*S*,8*S*,10a*R*,10b*S*)-7,8-Di(benzoyloxy)-6a-chloro-1,5,6,6a,7,8,9,10,10a,10b-decahydro[1,3]oxazolo[4,3-*a*]isoquinolin-3(3*H*)-one (**11b**)

To a solution of **9a** (2.6 g, 5.8 mmol) in dry CH_2Cl_2 (90 ml) under argon at 0 °C was added $AlCl_3$ (7.70 g, 57.6 mmol) in one portion. The reaction mixture was allowed to warm up to room temperature and stirred overnight. The excess of $AlCl_3$ was carefully quenched with water (50 ml). The organic layer was separated and the water layer extracted with CH_2Cl_2 (2 × 25 ml). The combined organic extracts were washed with brine and dried over anhydrous Na_2SO_4. The organic solvents were evaporated under reduced pressure and the residue was purified by flash chromatography on silica gel (1 : 1 ethyl acetate–hexanes) to afford 57% yield of the isomers **11a** and **11b** with a 3.7 : 1 ratio, respectively (HPLC ratio, 65 : 35 H_2O–MeCN).

Compound **11a**: m.p. 230–231 °C (dec.), $[\alpha]_D^{31}$ +93.9 ($CHCl_3$, *c* 1.22). ^{1}H NMR (500 MHz, $CDCl_3$): 1.47 (1 H, dq, *J* = 2.8 and 15.0); 1.97 (1 H, m); 2.00 (1 H, m); 2.10 (1 H, dq, *J* = 2.9 and 15.7); 2.29 (1 H, dt, *J* = 2.0 and 14.5); 2.30 (1 H, m); 2.66 (1 H, tt, *J* = 4.3 and 14.9); 3.16 (1 H, ddd, *J* = 2.7, 13.0 and 14.1); 3.82 (1 H, ddd, *J* = 1.6, 5.6 and 14.3); 4.02 (1 H, m); 4.05 (1 H, m); 4.49 (1 H, m); 5.69 (1 H, d, *J* = 4.0); 5.74 (1 H, q, *J* = 3.3); 7.37 (2 H, t, *J* = 7.8); 7.46 (2 H, t, *J* = 7.6); 7.54 (1 H, t, *J* = 7.5); 7.59 (1 H, t, *J* = 7.5); 7.96 (2 H, d, *J* = 8.3); 8.14 (2 H, d, *J* = 8.3). ^{13}C NMR ($CDCl_3$): 17.11, 24.35, 37.10, 38.20, 48.48, 52.92, 66.64, 67.30, 68.12, 69.29, 128.39, 128.45, 128.60, 129.69, 133.14, 133.62, 156.49, 165.46, 165.77. IR (KBr): 2 931, 1 761, 1 720, 1 450, 1 420, 1 268, 1 103, 1 068, 710. HRMS (FAB), *m/z* for $C_{25}H_{25}ClNO_6$ calculated (M^+) 470.1370; found: 470.1362. For $C_{25}H_{24}ClNO_6$ calculated: 63.90% C, 5.15% H, 2.98% N; found: 63.80% C, 5.17% H; 3.01% N.

Compound **11b**: m.p. 223–225 °C (dec.), $[\alpha]_D^{31}$ +12.8 ($CHCl_3$, *c* 0.72). ^{1}H NMR (500 MHz, $CDCl_3$): 1.68 (1 H, dt, *J* = 4.4 and 12.0); 1.74 (1 H, dddd, *J* = 3.4, 12.0, 12.0 and 12.0); 1.89 (1 H, dd, *J* = 3.3 and 13.7); 1.95 (1 H, td, *J* = 4.2 and 10.9); 1.96 (1 H, dddd, *J* = 4.5, 12.1, 12.1 and 12.9); 2.02 (1 H, ddd, *J* = 6.0, 13.2 and 13.8); 2.20 (1 H, dddd, *J* = 4.2, 4.5, 4.5 and 12.9); 3.43 (1 H, ddd, *J* = 3.3, 12.3 and 13.7); 3.81 (1 H, ddd, *J* = 5.6, 8.1 and 9.9); 3.88 (1 H, d, *J* =

5.2 and 13.7); 4.12 (1 H, dd, *J* = 5.5 and 8.8); 4.45 (1 H, t, *J* = 8.6); 5.77 (1 H, d, *J* = 2.5); 5.85 (1 H, ddd, *J* = 3.2, 4.5 and 12.1); 7.28 (2 H, t, *J* = 7.7); 7.47 (1 H, t, *J* = 7.5); 7.51 (2 H, t, *J* = 7.7); 7.65 (1 H, t, *J* = 7.4); 7.79 (2 H, d, *J* = 7.9); 8.03 (2 H, d, *J* = 7.6). ^{13}C NMR ($CDCl_3$): 21.53, 25.31, 34.54, 36.60, 43.14, 54.05, 65.59, 69.49, 72.52, 73.71, 128.30, 128.81, 129.04, 129.60, 129.75, 133.08, 133.84, 156.48, 165.20, 165.40. IR ($CHCl_3$): 2 936, 1 751, 1 728, 1 452, 1 277. LRMS (CI), *m/z* (%): 470 (M^+, 40), 312 (35), 190 (25), 105 (100).

(1*R*,6*S*)-2-(2-Bromoethyl)-6-(*tert*-butyldimethylsilyloxy)cyclohex-2-en-1-ol (**12a**)

To a stirred solution of the diol[8] **12** (1.63 g, 7.39 mmol) in dry CH_2Cl_2 (50 ml) under argon at –78 °C, was added *N*,*N*-diisopropylethylamine (2.70 ml, 15.5 mmol), resulting in a white suspension. After 10 min, *tert*-butyl(dimethyl)silyl triflate (1.87 ml, 8.13 mmol) was added dropwise, and stirring/cooling continued. After 5 h, excess of *tert*-butyl(dimethyl)silyl triflate (0.85 ml, 3.7 mmol) was added dropwise, and the stirred mixture was allowed to warm up to room temperature overnight. After 20 h, the reaction was quenched with water (80 ml) and saturated aqueous NH_4Cl (30 ml), and extracted with CH_2Cl_2 (4 × 80 ml). The combined organic fractions were dried over $MgSO_4$, filtered and the solvents were evaporated under reduced pressure to yield a brown oil. Purification by flash chromatography on silica gel (50 : 1 hexanes–ethyl acetate), afforded the title compound as a colorless oil in 70% yield, $[\alpha]_D^{25}$ –42.0 ($CHCl_3$, *c* 1.0). ^{1}H NMR (400 MHz, $CDCl_3$): 0.11 (6 H, s); 0.92 (9 H, s); 1.57 (1 H, m); 1.78 (1 H, m); 2.03 (1 H, m); 2.18 (1 H, m); 2.63 (2 H, m); 2.76 (1 H, m); 3.53 (2 H, m); 3.81 (1 H, dt, *J* = 10.6 and 3.7); 3.9 (1 H, t, *J* = 3.5); 5.65 (1 H, m). ^{13}C NMR (100 MHz, $CDCl_3$): –4.9, –4.5, 18.0, 23.9, 25.4, 25.7, 31.8, 38.4, 68.6, 70.7, 127.7, 134.7. IR (KBr): 3 560, 2 970, 2 930, 1 260, 1 100. HRMS (CI), *m/z* for $C_{14}H_{27}BrO_2Si$ calculated: 335.3550; found: 335.3550.

(3*S*,4*S*)-3-Benzoyloxy-2-(2-bromoethyl)-4-(*tert*-butyldimethylsilyloxy)cyclohex-1-ene (**13**)

To a stirred solution of the alcohol **12a** (4.61 g, 13.7 mmol) and benzoic acid (1.85 g, 15.1 mmol) in dry THF (12 ml) at 0 °C was added a solution of the Mitsunobu reagent, which was previously prepared by addition of DEAD (4.79 g, 27.5 mmol) to a stirred solution of Bu_3P (5.56 g, 27.5 mmol) in dry THF (12 ml) at 0 °C, and stirred at the same temperature for 20 min. The reaction mixture was then allowed to warm up to room temperature. After 16 h, the solvents were evaporated under reduced pressure to furnish yellow oil, which was pre-purified by passage through a silica plug with benzene. Purification by flash chromatography on silica gel (benzene) afforded the title compound in 84.7% yield, m.p. 65–66 °C, $[\alpha]_D^{25}$ +102.0 (CH_3, *c* 1.0). ^{1}H NMR (400 MHz, $CDCl_3$): 0.3 (3 H, s); 0.5 (3 H, s); 0.84 (9 H, s); 1.74 (1 H, m); 1.82 (1 H, m); 2.11 (1 H, m); 2.30 (1 H, m); 2.50 (1 H, m); 2.60 (1 H, m); 3.45 (2 H, m); 4.02 (1 H, ddd, *J* = 2.9, 4.73 and 7.02); 5.40 (1 H, d, *J* = 4.42); 5.84 (1 H, bt, *J* = 3.6); 7.45 (2 H, tm, *J* = 7.6); 7.57 (1 H, ddt, *J* = 1.38, 6.87 and 7.93); 8.05 (2 H, dm, *J* = 8.5). ^{13}C NMR (100 MHz, $CDCl_3$): –4.88, –4.86, 17.8, 22.1, 25.6, 27.2, 31.1, 37.5, 69.2, 73.4, 128.4, 129.7, 130.1, 130.3, 130.8, 133.0, 166.1. IR (KBr): 2 928, 2 858, 1 714, 1 258, 1 114, 836. HRMS (CI), *m/z* for $C_{21}H_{32}O_3BrSi$ calculated: 439.1304; found: 439.1291.

3-{2-[(5*S*,6*S*)-6-Benzoyloxy-5-(*tert*-butyldimethylsilyloxy)cyclohex-1-enyl]ethyl}-[1,3]oxazolidine-2,4-dione (**14**)

To a stirred solution of compound **13** (0.23 g, 0.52 mmol) in dry THF (5 ml) was added oxazolidine-2,4-dione (0.114 g, 1.05 mmol), followed by 1,1,3,3-tetramethylguanidine (0.13 ml, 1.05 mmol). The cloudy solution was refluxed for 48 h, and then filtered through celite. The solvents were evaporated under reduced pressure, and the residue was purified by flash chromatography on silica gel (hexanes) to furnish the title compound in 85% yield, m.p. 68–69 °C, $[\alpha]_D^{26}$ +80 (CH_2Cl_2, *c* 0.59). ^{1}H NMR ($CDCl_3$): –0.07 (3 H, s); –0.01 (3 H, s); 0.74 (9 H, s); 1.67–1.79 (2 H, m); 2.08–2.29 (4 H, m); 3.51–3.70 (2 H, m); 3.94 (1 H, m); 4.56 (2 H, s); 5.51 (1 H, d, *J* = 5.1); 5.66 (1 H, s); 7.38 (1 H, dd, *J* = 8.3); 7.47 (1 H, d, *J* = 7.6); 8.02 (1 H, d, *J* = 8.3). ^{13}C NMR ($CDCl_3$): –5.0, –4.9, 17.8, 22.7, 25.5, 28.0, 31.1, 38.9, 67.6, 69.9, 74.6, 128.1, 128.2, 129.4, 129.6, 130.1, 130.7, 132.9, 155.6, 166.0, 170.1. IR ($CDCl_3$): 2 953, 2 856, 1 817, 1 746, 1 602, 1 264. HRMS (CI), *m/z* for $C_{24}H_{34}NSiO_6$ calculated: 460.2155; found: 460.2144. For $C_{24}H_{34}NSiO_6$ calculated: 62.75% C, 7.19% H, 3.05% N; found: 62.96% C, 7.00% H, 3.04% N.

3-(2-(5*S*,6*S*)-6-Benzoyloxy-5-hydroxy-1-cyclohexeneyl)ethyl[1,3]oxazolidine -2,4-dione (**15**)

To a stirred solution of the **14** (1.1 g, 2.4 mmol) in MeOH (70 ml) was added concentrated HCl (1.5 ml). After 30 min, the solvents were evaporated under reduced pressure and the residue purified by flash chromatography on silica gel (3 : 1 hexanes–ethyl acetate) to afford a quantitative yield of the title compound, $[\alpha]_D^{25}$ +91.7 (EtOAc, *c* 2.3). ^{1}H NMR ($CDCl_3$): 1.78–2.35 (6 H, m); 2.95 (1 H); 3.73 (1 H, m); 3.95 (1 H, m); 3.98 (1 H, m); 4.62 (2 H, s); 5.58 (1 H, d, *J* = 5.1); 5.72 (1 H, s); 7.42 (2 H, t, *J* = 7.5); 7.55 (1 H, t, *J* = 8.5); 8.02 (2 H, d, *J* = 6.9). ^{13}C NMR ($CDCl_3$): 22.3, 26.7, 31.3, 38.4, 67.8, 69.4, 73.9, 128.3, 129.6, 129.7, 130.0, 130.5, 133.2, 155.8, 166.8, 170.6. IR (neat): 3 501, 2 932, 1 815, 1 730, 1 452, 1 271. HRMS (CI), *m/z* for $C_{18}H_{20}NO_6$ calculated: 346.1290; found: 346.1295.

3-(2-(5*S*,6*S*)-5,6-Dibenzoyloxy-1-cyclohexenyl)ethyl[1,3]oxazolidine-2,4-dione (**16**)

To a stirred solution of the alcohol **15** (0.70 g, 2.02 mmol), benzoic acid (0.50 g, 4.04 mmol), and catalytic amount of DMAP in dry CH_2Cl_2 (30 ml) at 0 °C was added a solution of DCC (0.83 g, 4.04 mmol) in dry $CHCl_2$ (3 ml). The reaction was allowed to warm up to room temperature overnight, and the solid was filtered through celite. The solvents were evaporated under reduced pressure and the residue was purified by flash column chromatography on silica gel (1 : 1 ethyl acetate–hexanes) to afford the title compound as a yellow oil in 77% yield, m.p. 51.5–52 °C, $[\alpha]_D^{26}$ +125.3 (CH_2Cl_2, *c* 2.16). ^{1}H NMR ($CDCl_3$): 1.95–2.41 (6 H, m); 3.67 (1 H, m); 3.80 (1 H, m); 4.63 (2 H, s); 5.38 (1 H, m); 5.80 (1 H, s); 6.05 (1 H, d, *J* = 5.2); 7.42 (6 H, m); 7.99 (4 H, m). ^{13}C NMR ($CDCl_3$): 23.1, 25.1, 31.0, 38.8, 67.8, 71.4, 72.8, 128.4, 128.5, 129.6, 129.7, 129.8, 129.9, 130.0, 131.2, 133.3, 155.8, 165.9. IR ($CHCl_3$): 1 743, 1 721, 1 450, 1 276, 1 108. HRMS (FAB), *m/z* for $C_{25}H_{24}NO_7$ calculated: 450.1553; found: 450.1558. For $C_{25}H_{24}NO_7$ calculated: 66.82% C, 5.12% H, 3.12% N; found: 67.09% C, 5.46% H, 3.06% N.

(6a*S*,7*R*,8*S*,10a*S*,10b*R*)-6a-Benzoyloxy-7,8-dihydroxy-1,5,6,6a,7,8,9,10,10a,10b-decahydro[1,3]oxazolo[4,3-*a*]isoquinolin-3(3*H*)-one (**19a**), (6a*S*,7*R*,8*S*,10a*S*,10b*R*)-7-Benzoyloxy-6a,8-dihydroxy-1,5,6,6a,7,8,9,10,10a,10b-decahydro[1,3]oxazolo[4,3-*a*]isoquinolin-3(3*H*)-one (**19b**) and (6a*S*,7*S*,8*S*,10a*S*,10b*R*)-7-Benzoyloxy-8-(1-*tert*-butyldimethylsilyloxy)-6a-hydroxy-1,5,6,6a,7,8,9,10,10a,10b-decahydro[1,3]oxazolo[4,3-*a*]isoquinolin-3(3*H*)-one (**19c**)

To a solution of compound **14** (0.17 g, 0.36 mmol) in MeOH (5 ml) at 0 °C was added $NaBH_4$ (0.14 g, 3.6 mmol) in one portion. The reaction was stirred for 30 min and quenched with acetone. The solvents were evaporated under reduced pressure and the residue extracted with ether (10 ml). The ether solution was then washed with brine (2 × 5 ml) and the solvents were evaporated under reduced pressure to afford compound **17** (0.14 g) in 82% crude yield. Compound **17** was used as crude material in the next step.

To a solution of **17** (0.14 g, 0.30 mmol) in dry CH_2Cl_2 (5 ml) under argon at 0 °C was added $BF_3{\cdot}Et_2O$ (0.39 ml, 3.0 mmol) dropwise. The reaction mixture was stirred at 0 °C for 1 h, and then allowed to warm up to room temperature overnight. The reaction was quenched with saturated $NaHCO_3$ solution (5 ml), washed with brine and dried over anhydrous Na_2SO_4. The solvents were evaporated under reduced pressure and the TLC analysis showed a complex mixture of products. Flash chromatography on silica gel (1 : 1 ethyl acetate–hexanes) led to the separation of eight products in a total of 55 mg. The three major products (**19a** : **19b** : **19c**, ratio of 7.3 : 3.3 : 1), making 84% of the total isolated mass, were identified.

Compound **19a**: m.p. 196–197 °C, $[\alpha]_D^{31}$ +1.44 ($CHCl_3$). ^{1}H NMR ($CDCl_3$): 1.5 (2 H, m); 1.9 (1 H, dt, *J* = 5.22 and 12.92); 2.05 (2 H, m); 2.4 (1 H, dd, *J* = 4.4 and 10.4); 2.89 (1 H, d, *J* = 12.91); 3.2 (1 H, dt, *J* = 2.75 and 13.73); 3.8 (2 H, m); 4.0 (3 H, m); 4.46 (1 H, t, *J* = 7.69); 7.48 (2 H, t, *J* = 7.69); 7.63 (1 H, t, *J* = 7.42); 7.98 (2 H, d, *J* = 7.42). ^{13}C NMR ($CDCl_3$): 19.62, 27.63, 29.01, 37.98, 44.64, 53.64, 66.45, 70.58, 72.71, 88.15, 128.65, 129.51, 129.89, 133.94, 156.75, 167.0. IR (KBr): 3 383, 3 050, 1 752, 1 267. LRMS (FAB), *m/z* (%): 348 (M^+, 5); 226 (100), 154 (30), 137 (25), 136 (25), 123 (20), 105 (25).

Compound **19b**: ^{1}H NMR ($CDCl_3$): 1.5 (4 H, m); 1.8 (1 H, d, *J* = 4.12 Hz); 1.98 (1 H, bs); 2.08 (1 H, bs); 2.22 (1 H, dt, *J* = 4.69 and 14.54); 3.24 (1 H, dt, *J* = 3.3 and 13.46); 3.84 (1 H, dd, *J* = 4.12 and 15.38); 4.26 (1 H, m); 4.44 (1 H, t, *J* = 7.69); 5.36 (1 H, d, *J* = 9.34); 7.5 (2 H, t, *J* = 7.42); 7.6 (1 H, t, *J* = 7.42); 8.1 (2 H, d, *J* = 7.14). ^{13}C NMR ($CDCl_3$): 19.30, 28.60, 29.68, 38.01, 45.93, 52.86, 66.48, 69.73, 73.71, 75.76, 128.68, 129.50, 129.89, 133.79, 156.6, 167.0. LRMS (FAB), *m/z* (%): 348 (M^+, 25), 219 (20), 155 (25), 154 (100), 149 (25), 137 (75), 136 (85), 107 (30), 105 (50).

Compound **19c**: ^{1}H NMR ($CDCl_3$): –0.2 (3 H, s); 0.0 (3 H, s); 0.68 (9 H, s); 1.6 (6 H, m); 1.9 (1 H, m); 2.15 (1 H, t, *J* = 14.28); 3.23 (1 H, dt, *J* = 3.02 and 13.73); 3.8 (1 H, dd, *J* = 3.84 and 14.29); 4.0 (2 H, m); 4.2 (1 H, m); 4.4 (1 H, t, *J* = 7.69); 5.38 (1 H, d, *J* = 9.06); 7.46 (2 H, t, *J* = 7.42); 7.58 (1 H, t, *J* = 7.42); 8.04 (2 H, d, *J* = 7.14). ^{13}C NMR ($CDCl_3$): –4.95, –4.38, 17.65, 19.22, 25.45, 29.59, 34.25, 38.06, 45.74, 52.81, 66.42, 70.16, 73.84, 75.19, 128.51, 129.50, 129.81, 133.45, 156.6, 167.0. LRMS (FAB), *m/z* (%): 462 (M^+, 20), 322 (20), 179 (50), 137 (15), 136 (15), 105 (100).

(6a*S*,7*R*,8*S*,10a*S*,10b*R*)-7,8-Di(benzoyloxy)-6a-hydroxy-1,5,6,6a,7,8,9,10,10a,10b-decahydro[1,3]oxazolo[4,3-*a*]isoquinolin-3(3*H*)-one (**20a**) and (6a*S*,7*R*,8*S*,10a*S*,10b*R*)-6a,8-Di(benzoyloxy)-7-hydroxy-1,5,6,6a,7,8,9,10,10a,10b-hydro[1,3]oxazolo[4,3-*a*]isoquinolin-3(3*H*)-one (**20b**)

To a solution of compound **16** (0.29 g, 0.66 mmol) in MeOH (5 ml) at 0 °C was added $NaBH_4$ (0.25 g, 6.6 mmol) in one portion. The reaction was stirred for 30 min and quenched with acetone. The solvents were evaporated under reduced pressure and the residue extracted with ether (10 ml). The ether solution was then washed with brine (2 × 5 ml) and the solvents were evaporated under reduced pressure to afford compound **18** (0.24 g) in 83% crude yield. Compound **18** was used as crude material in the next step.

To a solution of the crude **18** (0.24 g, 0.53 mmol) in dry CH_2Cl_2 (10 ml) under argon at 0 °C was added $BF_3{\cdot}Et_2O$ (0.68 ml, 5.3 mmol) dropwise. The reaction mixture was stirred at 0 °C for 1 h, and then allowed to warm up to room temperature overnight. The reaction was quenched with saturated $NaHCO_3$ solution (5 ml), washed with brine, and dried over anhydrous Na_2SO_4. The organic solvents were evaporated under reduced pressure and the residual mixture of products was purified by flash chromatography on silica gel (1 : 1 ethyl acetate–hexanes). Four products in a total of 174 mg were isolated. The two major products (**20a** : **20b**, ratio of 1.4 : 1), which represent 70% of the total isolated mass, were identified.

Compound **20a**: m.p. 195.5–196 °C, $[\alpha]_D^{30}$ +60.2 ($CHCl_3$, *c* 0.97). ^{1}H NMR (500 MHz, $CDCl_3$): 1.41 (1 H, ddd, *J* = 3.0, 5.0 and 14.9); 1.51 (1 H, td, *J* = 5.5 and 13.3); 1.63 (1 H, dddd, *J* = 5.5, 10.0, 14.4 and 14.7); 1.75 (1 H, ddd, *J* = 1.6, 3.1 and 13.5); 1.80 (1 H, dd, *J* = 4.6 and 11.3); 2.20 (1 H, ddt, *J* = 1.6, 4.7 and 14.4); 2.31 (1 H, tt, *J* = 4.7 and 14.5); ≈2.70 (OH, bs); 3.21 (1 H, td, *J* = 3.1 and 13.7); 3.80 (1 H, ddd, *J* = 1.6, 5.5 and 14.3); 3.94 (1 H, dd, *J* = 5.1 and 8.4); 3.98 (1 H, ddd, *J* = 5.0, 7.8 and 12.0); 4.39 (1 H, t, *J* = 8.1); 5.64 (1 H, td, *J* = 4.8 and 9.9); 5.67 (1 H, d, *J* = 10.2); 7.21 (2 H, t, *J* = 7.6); 7.24 (2 H, t, *J* = 7.8); 7.38 (2 H, t, *J* = 7.7); 7.78 (2 H, d, *J* = 8.3); 7.88 (2 H, d, *J* = 8.3). ^{13}C NMR ($CDCl_3$): 19.09, 25.64, 33.79, 38.0, 45.67, 52.81, 66.51, 72.20, 72.48, 73.46, 128.28, 128.42, 128.69, 129.46, 129.72, 133.05, 133.49, 156.81, 165.98, 166.08. IR (KBr): 3 511, 3 434, 1 748, 1 732, 1 698, 1 278, 1 112. LRMS (EI), *m/z* (%): 452 (M^+, 5), 407 (10), 346 (15), 310 (13), 286 (70), 208 (40), 105 (100).

Compound **20b**: m.p. 141–142 °C, $[\alpha]_D^{30}$ +42.6 ($CHCl_3$, *c* 0.97). ^{1}H NMR (500 MHz, $CDCl_3$): 1.54 (1 H, ddd, *J* = 3.0, 5.6 and 14.4); 1.75 (1 H, dddd, *J* = 5.6, 11.1, 14.1 and 14.2); 2.10 (1 H, tt, *J* = 4.7 and 14.4); 2.16 (1 H, dddd, *J* = 3.0, 4.7, 4.9 and 14.1); 2.28 (1 H, td, *J* = 5.9 and 13.0); 2.75 (1 H, ddd, *J* = 1.5, 3.3 and 13.0); 2.81 (1 H, dd, *J* = 4.6 and 10.8); 3.16 (1 H, ddd, *J* = 3.3, 13.3 and 14.2); 3.81 (1 H, s); 4.00 (1 H, ddd, *J* = 1.6, 5.7 and 14.0 Hz); 4.02 (1 H, m); 4.02 (1 H, m); 4.04 (1 H, m); 4.17 (1 H, d, *J* = 10.2); 4.46 (1 H, m); 5.43 (1 H, ddd, *J* = 1.9, 10.2 and 11.); 7.45 (2 H, t, *J* = 7.9); 7.49 (2 H, t, *J* = 7.9); 7.58 (1 H, t, *J* = 7.6); 7.62 (1 H, t, *J* = 7.4); 8.03 (2 H, d, *J* = 7.9); 8.08 (2 H, d, *J* = 7.9). ^{13}C NMR ($CDCl_3$): 19.68, 25.75, 27.98, 38.03, 42.67, 53.48, 66.53, 70.72, 73.71, 87.87, 128.42, 128.69, 129.71, 129.84, 133.24, 133.76, 156.65, 166.02, 166.80. IR (KBr): 3 414, 2 932, 1 749, 1 708, 1 450, 1 314, 1 273, 1 109. HRMS (FAB), *m/z* for $C_{25}H_{25}NO_7$ calculated: 452.1709; found: 452.1691.

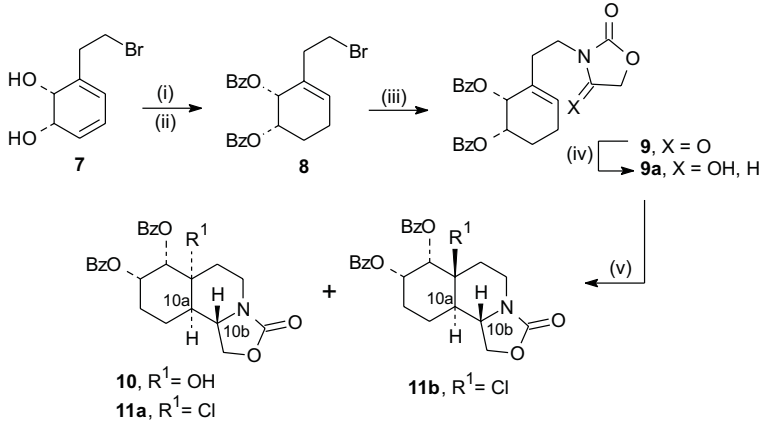
(6a*S*,7*R*,8*S*,10a*S*,10b*R*)-7,8-Di(benzoyloxy)-6a-chloro-1,5,6,6a,7,8,9,10,10a,10b-decahydro[1,3]oxazolo[4,3-*a*]isoquinolin-3(3*H*)-one (**21**)

To a solution of the crude **18** (0.21 g, 0.47 mmol) in dry CH_2Cl_2 (5 ml) under argon at 0 °C was added $AlCl_3$ (0.63 mg, 4.7 mmol) in one portion. The reaction mixture was stirred and

allowed to warm up to room temperature overnight. The excess of $AlCl_3$ was carefully quenched with water (3 ml). The organic layer was separated and the water layer extracted with CH_2Cl_2 (2 × 5 ml). The combined organic extracts were washed with brine and dried over anhydrous Na_2SO_4. The organic solvents were concentrated under reduced pressure and the crude material was purified by flash chromatography on silica gel (7 : 3 ethyl acetate–hexanes) to afford 70% yield of the title compound as a single isomer: m.p. 215–217 °C, $[\alpha]_D^{30}$ +81.8 ($CHCl_3$, *c* 1.01). ^{1}H NMR (500 MHz, $CDCl_3$): 1.59 (1 H, d, *J* = 14.9); 1.72 (1 H, qd, *J* = 5.2 and 13.1); 2.03 (1 H, td, *J* = 5.4 and 13.5); 2.19 (1 H, dd, *J* = 4.3 and 11.2); 2.22 (1 H, d, *J* = 13.9); 2.37 (1 H, m); 2.50 (1 H, tt, *J* = 4.7 and 14.9); 3.34 (1 H, td, *J* = 3.3 and 13.6); 3.84 (1 H, dd, *J* = 5.1 and 13.9); 4.02 (1 H, dd, *J* = 4.9 and 9.0); 4.14 (1 H, ddd, *J* = 5.2, 8.1 and 11.6); 4.47 (1 H, t, *J* = 8.4); 5.67 (1 H, td, *J* = 5.5 and 10.5); 5.90 (1 H, d, *J* = 9.7); 7.32 (2 H, t, *J* = 7.6); 7.38 (2 H, t, *J* = 7.6); 7.46 (1 H, t, *J* = 7.6); 7.51 (1 H, t, *J* = 7.6); 7.86 (2 H, d, *J* = 7.6); 8.01 (2 H, d, *J* = 7.6). ^{13}C NMR ($CDCl_3$): 20.07, 25.58, 36.28, 38.10, 48.18, 53.13, 66.39, 70.20, 72.64, 72.99, 128.27, 128.45, 128.72, 129.43, 129.87, 133.08, 133.62, 156.48, 165.58, 166.04. IR (KBr): 3 058, 2 944, 1 763, 1 722, 1 447, 1 318, 1 271, 708. LRMS (CI), *m/z* (%): 470 (M^+, 40); 390 (35), 308 (25), 190 (25), 105 (100). For $C_{25}H_{24}ClNO_6$ calculated: 63.90% C, 5.15% H, 2.98% N; found: 63.88% C, 5.20% H, 3.01% N.

RESULTS AND DISCUSSION

Biooxidation of (2-bromoethyl)benzene with *E. coli* JM109 (DTG601, ref.[9]) gave a remarkably high yield of the dienediol[8] **7** (8 g/l), which was chosen as the starting material for the preparation of both series of benzoate-protected diols (Scheme 2). The reduction of the less substituted double



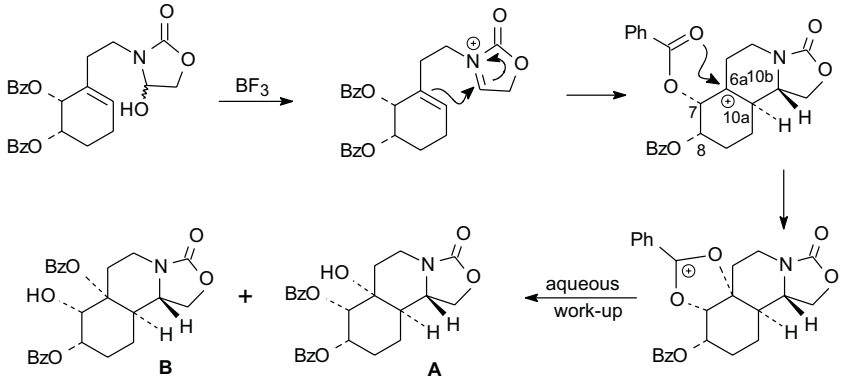
(i) PAD/AcOH/MeOH, 80% yield; (ii) PhCOOH/DCC/DMAP/CH_2Cl_2, 83% yield; (iii) oxazolidione/1,1,3,3-tetramethylguanidin/THF/reflux, 77% yield; (iv) $NABH_4$/MeOH, 80% yield; (v) BF_3/CH_2Cl_2, 55% yield or $AlCl_3/CH_2Cl_2$, 57% yield.

SCHEME 2

bond with potassium azodicarboxylate[8] (PAD) in AcOH followed by esterification of the two hydroxyls with DCC, $PhCO_2H$ in CH_2Cl_2 afforded dibenzoate **8** in 66% overall yield. Biooxidation and reduction with PAD are described in the literature[8,9].

cis-Series. Displacement of bromine with oxazolidine-2,4-dione in the presence of 1,1,3,3-tetramethylguanidine (TMG) in THF, followed by reduction of the more reactive amide carbonyl with $NaBH_4$ gave the hemiaminal **9a** in 80% yield. The *N*-acyliminium ion-olefin cyclization was performed with two different Lewis acid, $BF_3{\cdot}Et_2O$ and $AlCl_3$ in CH_2Cl_2 (Scheme 2). The use of BF_3 led to the isolation of the perhydroisoquinoline **10** in 55% yield as the only product of the reaction. With $AlCl_3$ under the same conditions, a mixture of the isomers **11a** and **11b** was isolated in 57% in a ratio of 3.7 : 1, respectively (*via* HPLC). The structures of all three compounds were determined by X-ray crystallography. All three compounds have the stereogenic center C-10b (corresponding to C-9 of morphine) set in the correct absolute sense and C-10a (C-14 of morphine) in the *epi*-configuration.

A proposed mechanism for the BF_3-induced cyclization is outlined in Scheme 3. After the initial formation of the carbocation, a neighboring group participation of the benzoate carbonyl[10] affords a *cis*-acetal carbo-

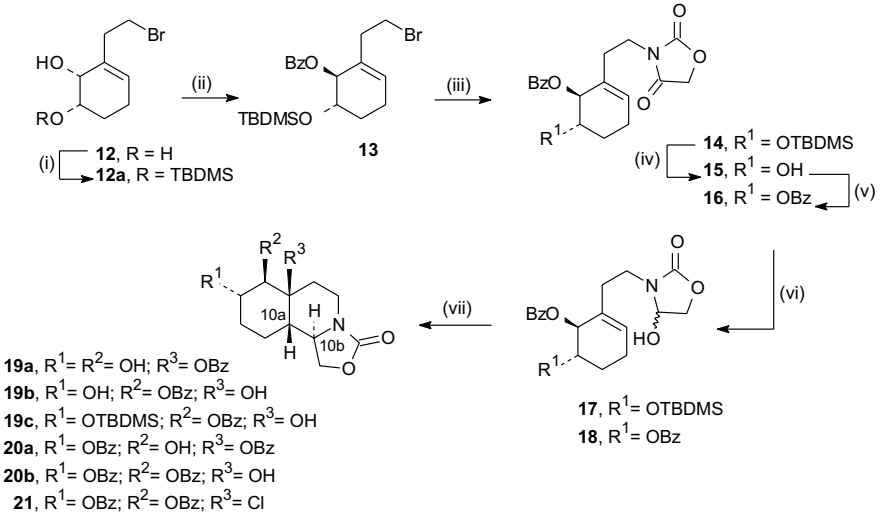


SCHEME 3

cation. This intermediate gave, after aqueous work-up, two *cis*-fused derivatives **A** and/or **B**. Based on this mechanism, the products of the reaction should have a *cis* relationship between C-6a/C-7 and C-6a/C-10a. Another indication that the reaction involves a *syn*-cyclic transition state is the isolation of product **B**. The stereochemistry of the ring junction in **10** is *cis*, indicating neighboring participation of the benzoate group in the cyclization

step. The stereochemistry of the ring junction in compounds **11a**/**11b** shows that chloride can be delivered from both sides of the molecule after the carbocation is formed. However, based on the isomer ratio, we can assume that the Lewis acid coordinates with the benzoate group delivering the chloride preferentially from the bottom side.

trans-Series. In an attempt to also set in the absolute stereochemistry of the stereocenter C-10a corresponding to C-14 of natural morphine, we developed a *trans*-series and performed the same cyclization reaction in the benzoate-protected diol **17** and **18** (Scheme 4). The *trans*-dibenzoates were prepared by the protection of the distal hydroxyl group in diol **12** as a silyl



(i) *tert*-Butyl(dimethyl)silyl triflate/*N,N*-diisopropylethylamine/CH_2Cl_2, 70% yield; (ii) PhCOOH/DEAD/Bu_3P/THF, 84% yield; (iii) oxazolidione/1,1,3,3-tetramethyguanidine/THF/reflux, 85% yield; (iv) HCl/MeOH, quantitatitative yield; (v) PhCOOH/DCC/DMAP/CH_2Cl_2, 77% yield; (vi) $NaBH_4$/MeOH, 77% yield; (vii) $BF_3{\cdot}Et_2O$ or $AlCl_3/CH_2Cl_2$

SCHEME 4

ether followed by the Mitsunobu inversion of the allyl hydroxyl group to furnish **13** in 59% overall yield. Substitution with oxazolidine-2,4-dione in the presence of TMG afforded the *N*-acyl derivative **14** in 85% yield. Deprotection of the distal silyl ether in acidic conditions, followed by esterification with DCC, $PhCO_2H$ in CH_2Cl_2 furnished *N*-acyl dibenzoate protected diol **16** in 77% overall yield from **14**. Reduction of the more reactive carbonyl in imides **14** and **16** afforded the precursors for cyclization, **17** and **18**, respectively.

Substrate **17** was then reacted with $BF_3 \cdot Et_2O$ under conditions identical to those in the *cis*-series and afforded a complex mixture of isomers. The three major products were isolated and identified as **19a**, **19b** and **19c** in a ratio of 7.3 : 3.3 : 1, representing 84% of the total isolated mass (Scheme 4). The stereochemistry of the isomer **19a** was assigned by X-ray[11] and the others by NMR (ref.[12]). As expected, the stereochemistry of the stereocenter corresponding to the C-14 of natural morphine has been set in the absolute sense. However, C-10b (C-9 of natural morphine) was set in the *epi*-configuration. The identification of adduct **19a** is in total agreement with the proposed *N*-acyliminium ion cyclization mechanism described in Scheme 3.

With the stereochemistry at C-10a set in correctly in the cyclization of **17**, and the suspicion that the silyl ether group was reacting with the BF_3 affording a complex mixture of products, we turned to the cyclization of **18** with BF_3 and $AlCl_3$. As expected, reaction of hydroxycarbamate **18** with $BF_3 \cdot Et_2O$ furnished a cleaner mixture of isomers. The two major isomers **20a** and **20b** (1.4 : 1), representing 70% of the total isolated mass of compounds, were separated (HPLC) and identified (Scheme 4). The stereochemistry of both diastereoisomers was assigned by X-ray[11] and 2D NMR. The isolation of the adducts confirmed again the benzoate neighboring group participation in the mechanism of the reaction. When the same substrate was reacted with $AlCl_3$, compound **21** was isolated in 70% yield as the only isomer of the reaction. The stereochemistry was proven by X-ray[11] and 2D NMR. The stereochemistry results from the *trans*-series bode well for the versatility of the approach to morphinans. Simple chemical manipulations of tricyclic compounds **20a**, **20b** or **21** can lead to the synthesis of both morphine enantiomers. For example, to approach natural morphine synthesis, the stereochemistry at C-7 and C-10b would be inverted. On the other hand, C-7 and C-10b have the correct stereochemistry for the *ent*-morphine synthesis, provided dehydrochlorination or dehydration reaction of C-6a/C-10a is performed to intercept an intermediate similar to **1**. In the *cis*-series, similar arguments also lead to design of improved approaches to isoquinoline derivatives **1** and **2**, suitable for the next generation attempts at morphinans.

Acid-catalyzed cyclization of the precursors **9a** (*cis*-series) and **18** (*trans*-series) demonstrated good stereoselectivities in the formation of stereocenters C-6a, C-10a and C-10b. The only noted exception was the case of **9a** when $AlCl_3$ was used, and **11b** was formed as a minor product. The observed stereospecificity of the cyclization reactions has important implications in the stereocontrolled synthesis of morphine and morphine alkaloid derivatives. With the stereoselective cyclization as the key step, synthons **1** and **2**

can both be accessed from cyclization precursors **18** and **9a**, respectively. Thus the results reported in this paper confirmed better preparation of both **1** and **2**. In addition, the tin-mediated cyclization of low stereospecificity reported previously has been replaced by a more environmentally friendly acid-catalyzed protocol. Finally, in the fully saturated tricyclic compounds **10**, **11a**, **11b**, **20a**, **20b** and **21**, the C-14 center of both morphine and *ent*-morphine can be controlled at will, albeit at the expense of the corresponding C-9 stereochemistry. The results of further applications will be reported in due course.

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