Synthesis of the Tetracyclic Bis(acetal) Lactone Portion of Saudin

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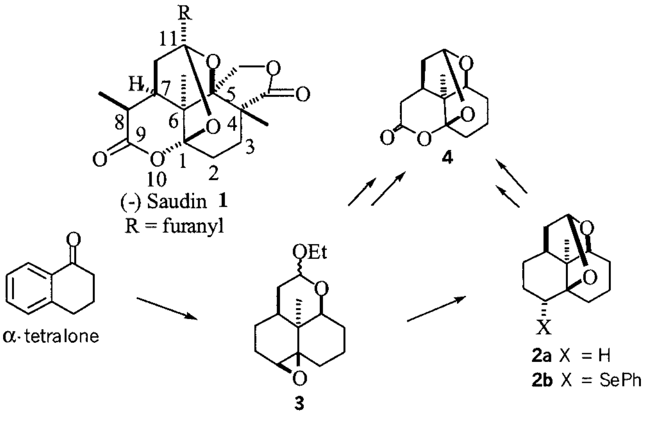
Two synthetic approaches towards the synthesis of the tetracyclic lactone **4**, containing the caged bis(acetalic) backbone of Saudin, were explored. Both sequences included the utilization of the known epoxy-acetal **3**, prepared stereoselectively by means of an intramolecular radical cyclization, as the common key intermediate, allowing total control over the relative stereochemistry of four consecutive chiral centers. Oxidative degradation with ruthenium dioxide and unsymmetrical ozonolysis reactions provided the new two key synthons in each synthetic route.

Introduction

In continuation of our efforts toward the intermediate synthesis of polyoxygenated natural products,[1−3] we have for some time been interested in the structural features of Saudin (**1**; Scheme 1), particularly in the construction of its highly oxygenated, uncommon, and attractive bis(acetal) substructure. This natural product, exhibiting important hypoglycemic activity, was isolated from the leaves of the toxic plant *Cluytia richardiana* in 1985.[4,5] In recent years, related synthetic studies have been published,[6−10] including a racemic total synthesis,[11] and more recently, Boeckman's research group has achieved the first enantioselective total synthesis of (+)- and (−)-Saudin, establishing its absolute configuration.[12]

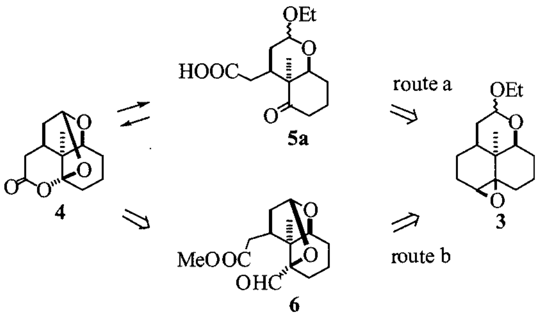


Scheme 1. Synthesis of precursors

In our previous work,[9] we have reported the synthesis of compound **2b** starting from α-tetralone (Scheme 1), which structurally resembles the caged acetalic backbone of the natural product. We also showed that the introduction of stereochemistry of the four consecutive stereocenters at the carbon atoms 1, 5, 6, and 7 on the tricyclic compound **3** can be easily controlled after the Birch alkylation reduction of the aromatic α-tetralone.[9a]

In this contribution, we have developed two different strategies for the stereoselective synthesis of the tetracyclic δ-lactone **4** as the bis(acetalic) lactone subunit of the natural product's main framework.

Both approaches were performed by starting from the already known epoxy-acetal **3**, as outlined in Scheme 2. The first synthetic route − route a − is based on our assumption that the open bicyclic oxo acid **5a**, possessing all the functional groups and the required stereochemistry, should eventually equilibrate into the lactone **4**, as in natural Saudin. Furthermore, molecular model analysis of **5a** shows a considerable increase in its flexibility with respect to its tricyclic precursor and this seemed encouraging when we con-



Scheme 2. Retrosynthetic analyses of alternative routes toward the bis(acetal) lactone portion **4** of Saudin

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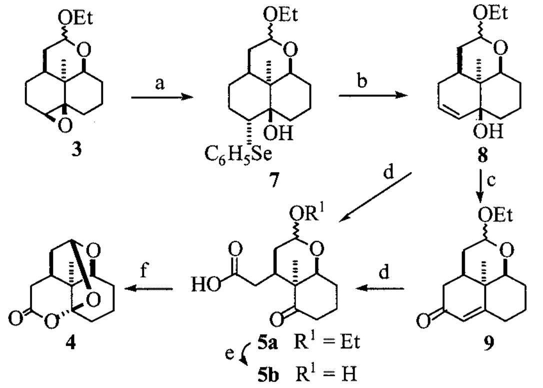
sidered that, once the acetal hydrolysis had occurred, the enhanced flexibility should provide for an easier hemiacetal ketone approach in order to form the intramolecular bis(acetal) unit.

The second synthetic strategy, represented by route b, involves the early formation of a caged acetal moiety such as **6** through an unsymmetric ozonolysis, followed by appropriate modifications of the formyl ester that could provide the lactone ring. We anticipated from our previous experience[9] that this advanced acetal would most probably remain intact, holding the conformation in place through the lactone formation.

Results and Discussion

As outlined in Scheme 3, the synthesis began with selenium dioxide elimination[13,14] from the selenide **7**,[9,15,16] followed by oxidative rearrangement[17] of the allylic alcohol **8** by treatment with pyridinium chlorochromate. This gave rise to the α,β-unsaturated ketone **9**, which was isolated pure in good yield (92%). With this compound to hand, we next investigated functional group manipulations on it for the formation of the tetracyclic skeleton **4**.



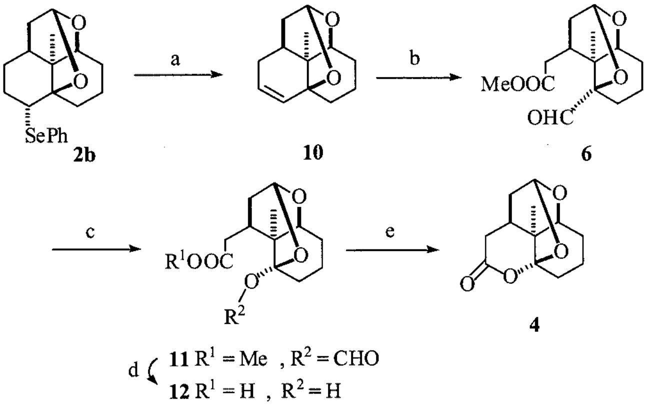
Scheme 3. Route a for the synthesis of **4**; reagents and conditions: a) $(PhSe)_2/NaBH_4/EtOH$, reflux; b) 30% $H_2O_2/NaHCO_3/THF$, room temp.; c) $PCC/Al_2O_3/CH_2Cl_2$, room temp.; d) $RuO_2{\cdot}H_2O/NaIO_4/CH_3CN/CCl_4/H_2O$, room temp.; e) 6 N $HCl/THF/H_2O$, 70 °C; f) cat. *p*TsOH/toluene, MS (4 Å), room temp.

We first considered oxidative degradation of the olefinic bond of **9**. This compound was resistant toward ozonolysis or osmium tetroxide/sodium periodate[18] procedures, but the process worked well when the ruthenium dioxide/periodate method[19] was used, affording the oxo acid **5a** in quantitative yield. Moreover, the best results were found when that procedure was directly applied upon the allylic alcohol **8** to produce the same oxo acid **5a**.

In view of the successful transformation of the acetal reactant mixture **7** into a single tetracyclic compound **2b**[9,20] with *p*-toluenesulfonic acid in toluene at room temperature, we envisaged this as an alternative reaction for the sequence path from **5a** to **4**.

Considerable experimentation was carried out into one-pot procedures for the spontaneous formation of **4**. Neither acetal hydrolysis, nor the new intramolecular bis(acetal) formation and further lactonization needed for the conversion of open oxo acid **5a** into its cyclic form **4** were as easy or as successful to accomplish as we had expected. In practice, a variety of acid catalysis conditions − amongst others, *p*TsOH or TFA in toluene or benzene, with or without water, or addition of molecular sieves at room temperature or under reflux − were unable to achieve the desired cyclization. We finally succeeded in the elaboration of the desired lactone **4** by a two-step sequence that involved acetal hydrolysis of **5a** under classical acidic conditions (HCl, THF, H_2O) to give the hemiacetal acid **5b**. Then, with catalytic *p*-toluenesulfonic acid in toluene and the presence of molecular sieves for 5 d at room temperature, the intramolecular formation of the acetal took place on the β-face and the C-5 hemiacetalic hydroxy group derived from a carbonyl group reacted by trapping the carboxyl group to form the δ-lactone. Finally, by careful preparative chromatography, compound **4** was isolated in pure form in 70% yield together with another fraction as a complex mixture of products.

At the same time, we explored route b and focused our attention to the early formation of the caged tetracyclic acetal moiety through the formation of olefinic acetal **10**, as illustrated in Scheme 4.



Scheme 4. Route b for the synthesis of **4**; reagents and conditions: a) 30% H_2O_2, $NaHCO_3$, THF, room temp., b) O_3, $NaHCO_3$, $CH_2Cl_2/MeOH$, −78 °C, then Ac_2O, Et_3N, room temp., c) *m*CPBA, $NaHCO_3$, CH_2Cl_2, 0 °C, d) LiOH, EtOH, room temp., e) DCC, DMAP, CH_2Cl_2, room temp.

The epoxy-acetal **3** was again selected as a convenient precursor for the cyclic bis(acetal) selenide **2b**,[9] through a regioselective epoxide opening with diphenyl diselenide/sodium borohydride followed by a *trans*-acetalation of **7** under *p*-toluenesulfonic acid catalysis. Treatment of **2b** with hydrogen peroxide and solid $NaHCO_3$ in THF at room temperature allowed ready access to the compound **10** (92%). This rigid bis(acetal) skeleton was viewed as the direct tetracyclic precursor of **4** through an unsymmetrical ozonolysis reaction, the ozonolytic cleavage of **10** to obtain both the formyl and α-alkoxy hydroperoxide groups at the sp^2-carbon atoms being based on the pioneering work of Schreiber[21] and further reports[22] on cycloenes.

Our main objective was to address the regioselectivity of positions of both methoxycarbonyl and formyl groups in that olefinic acetal **10**. It was therefore necessary to perform the reaction in CH_2Cl_2/MeOH, buffered with $NaHCO_3$, followed by manipulation of the peroxide with Ac_2O/Et_3N. In the event, the reaction occurred with fragmentation of the primary ozonide in an exclusive and regioselective way to give only one of the two possible regioisomers, the formyl ester **6** (78%). This experimental evidence suggests that the cleavage of the substituted ozonide may be controlled by the electronic effects of the acetalic oxygen atom bonded to the allylic position. In this sense, Schreiber et. al. have observed similar results on allylic acetates.[21]

The structure of **6** was confirmed by ^1H and ^{13}C NMR spectroscopy. The ^1H NMR spectrum showed the expected number and patterns of signals consistent with that structure, mainly the signals at $\delta = 3.65$ (methyl ester) and 9.82 ppm (formyl group) replacing the olefinic protons, and the fact that the formyl proton is a singlet indicates that the carbon atom of the formyl group is attached to a quaternary carbon atom, as in structure **6**. Accordingly, its ^{13}C NMR spectrum displays two peaks at $\delta = 172.55$ and 205.78 ppm as expected for the two carbonyl groups, ester and formyl functionality, together with the methoxy group signal at $\delta = 51.77$ ppm. The peaks corresponding to the carbon atoms involved in the acetal unit were shifted downfield, and the quaternary carbon atom β to the formyl group was shifted downfield to $\delta = 36.10$ ppm with respect to the corresponding signal at $\delta = 31.12$ ppm in olefinic acetal **10**.

The conversion of the formyl moiety into a formate moiety (**6** →**11**) was accomplished through a Baeyer−Villiger oxidation[23] in heterogeneous phase with *m*CPBA and $NaHCO_3$ in CH_2Cl_2, and the resulting diester **11** was obtained in quantitative yield. This transformation is clearly shown by the ^1H NMR upfield shift of the formyl proton signal from $\delta = 9.82$ to $\delta = 8.46$, a characteristic value for a formate, as well as the ^{13}C NMR carbonyl shift from $\delta = 205.78$ to $\delta = 159.86$ ppm. It is also indicated by the downfield shift of the newly formed acetalic carbon atom going from $\delta = 82.78$ ppm to $\delta = 106.89$ ppm.

With the diester **11** now available, we undertook the formation of the lactone ring by hydrolysis of the ester function and subsequent cyclization. Treatment of **11** with $NaOCH_3/CH_3OH$ provided a mixture of products derived from ester mono- and dihydrolysis. Acetal opening was also observed. Similarly, the hydrolysis of both esters was observed in all attempts with NaOH/EtOH or KOH/EtOH, and identical results were obtained when *p*-toluenesulfonic acid in benzene was used. Therefore, to avoid the acetal opening assisted by the C-5 hydroxy group in reactions in the presence of sodium or potassium, we decided to use lithium hydroxide. Thus, compound **12** was obtained in 92% yield by treatment of the diester **11** with LiOH/EtOH at room temperature. In the ^1H NMR spectrum of the crude **12**, the 2-H proton appears at $\delta = 5.30$ ppm as a broad doublet, and a broad singlet at $\delta = 3.73$ is shown for the 8a-H. No signals for protons corresponding to the methoxycarbonyl and formyl groups were observed.

Finally, the conformational rigidity conferred by the extra ring allowed the final transformation to be carried out successfully, affording the lactone **4** in 85% yield by a room-temperature DCC/DMAP[24]-catalyzed intramolecular lactonization. The complete assignment of the spectra was accomplished by a correlation between the ^{13}C NMR values of **4** and the most significant carbon values reported for Saudin.

Conclusions

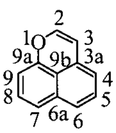
We have developed two different stereoselective linear sequences for the synthesis of the tetracyclic lactone framework **4**, present in Saudin, both starting from a common precursor epoxy-acetal **3**, derived from α-tetralone. Route a involved the synthesis of the open precursor of the lactone and required a series of hydrolysis/cyclization reactions in an equilibration process toward the final bis(acetal) lactone. However the equilibration did not take place as we expected and the desired product was obtained in pure form, together with a complex mixture of by-products. On the other hand route b featured the early formation of a tetracyclic acetal, followed by an unsymmetrical ozonolysis to generate the bifunctional formyl/methoxycarbonyl product in a regiocontrolled manner. A regioselective Baeyer−Villiger oxidation followed by hydrolysis afforded the second hemiacetal with the proper stereochemistry. Lactonization through the use of DCC/DMAP produced the final product in good yield.

In conclusion, we have also shown that, in the formation of cage-like acetals, the more flexible bicyclic systems tend to favor the cyclization processes, besides affording undesired products whereas the tricyclic, conformationally locked systems proceeded smoothly toward the final lactone.

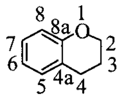
Experimental Section

General Remarks: Melting points were determined with an Ernst Leitz hot-stage microscope and are uncorrected. TlC analyses were performed on aluminum foil plates coated with 0.1 mm Merck silica gel 60 GF254. Flash chromatography was performed with 300−400 mesh silica gel under slight nitrogen pressure, with increasing EtOAc/hexanes gradients as solvents. Commercial reagents and solvents were of analytical grade or purified by standard procedures prior to use. All reactions involving air- or moisture-sensitive materials, were carried out under nitrogen. IR spectra were recorded with a Bruker FT I-25 spectrophotometer, as liquid films in NaCl for oils and KBr disks for solids. NMR experiments were run in $CDCl_3$ at 200.1 MHz for ^1H NMR and at 50.3 MHz for ^{13}C NMR with a Bruker Ac-200E NMR spectrometer and referenced to the solvent as the internal standard. The carbon type was determined by DEPT experiments. GC-MS analyses were carried out with a Perkin−Elmer Autosystem XL Gas Chromatograph

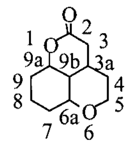
Turbo Mass machine equipped with a 240°C injector, with an Elite 1 100% dimethylpolysiloxane column, and the products were identified by their retention times. Mass spectra (MS) and high-resolution mass spectra (HRMS) were recorded at the UCR Mass Spectrometry Facility, Department of Chemistry, University of California, USA, and elemental analyses were recorded at Atlantic Microlab, Inc, Georgia, USA. To describe the spectroscopic data for the compounds we used the numbering of the following base compounds:



Compounds **8, 9, 10**



5a, 6, 11, 12



4

Allyl Alcohol 8: A solution of selenyl alcohol **7**, obtained according to ref.[9] (172 mg; 0.42 mmol) with sodium hydrogen carbonate (96 mg; 1.15 mmol) in THF (5 mL), was prepared and maintained at 0 °C. Hydrogen peroxide (30%, 0.53 mL; 5.84 mmol) was added and the solution was stirred at room temperature overnight. The reaction mixture was poured into brine (30 mL) and extracted with Et_2O (3 × 15 mL). The combined organic extracts were washed with water, dried with anhydrous sodium sulfate, and decanted, and the solvents were evaporated. Purification of the crude oil by column chromatography gave the acetals **8** (100 mg; 94%) as a colorless oil. **8a (*α*-acetal):** ^{1}H NMR ($CDCl_3$, 200 MHz): δ = 5.65 (br. d, J = 11 Hz, 1 H, 5-H), 5.60 (dd, J_1 = 11 and J_2 = 1.6 Hz, 1 H, 6-H), 4.92 (d, J = 4.22 Hz, 1 H, 2-H), 4.61 (s, 1 H, OH), 3.89 (br. s, 1 H, 9a-H), 3.65 (dq, J_1 = 9.6 and J_2 = 7.04 Hz, 1 H, OCH_2CH_3), 3.45 (dq, J_1 = 9.6 and J_2 = 7.00 Hz, 1 H, OCH_2CH_3), 2.63 (dt, J_1 = 14.3 and J_2 = 10.1 Hz, 2 H, 3-H), 2.03−1.51 (m, 9 H, 3a-H,4,7,8,9), 1.23 (t, 3 H, J_1 = 7.1 Hz, OCH_2CH_3), 0.94 (s, 3 H, 9b-methyl) ppm. ^{13}C NMR ($CDCl_3$, 50 MHz): δ = 131.43 (C-6), 127.74 (C-5), 97.88 (C-2), 71.57 (C-6a), 71.57 (C-9a), 62.48 (OCH_2CH_3), 36.05 (C-9b), 35.14 (C-4), 33.20 (C-3), 32.08 (C-3a), 28.87 (C-7), 25.20 (C-9), 22.94 (C-9b methyl), 16.23 (C-8), 14.95 (OCH_2CH_3) ppm. **8b (*β*-acetal):** IR (KBr): $\tilde{\nu}$ = 3470, 2926, 2884, 1650, 1460, 1388, 1358, 1246, 1140, 1070, 1022, 952, 718, 620 cm^{-1}. ^{1}H NMR ($CDCl_3$, 200 MHz): δ = 5.65 (br. d, J = 10.5 Hz, 1 H, 5-H), 5.61 (br. d, J = 10.5 Hz, 1 H, 6-H), 4.53 (dd, J_1 = 10.2 and J_2 = 2.8 Hz, 1 H, 2-H), 4.50 (dd, 1 H, OH), 3.89 (m, 1 H, OCH_2CH_3), 3.53 (m, 1 H, OCH_2CH_3), 3.44 (br. s, 1 H, 9a-H), 2.42−2.30 (m, 2 H, 3-H), 1.99−1.53 (m, 9 H, 3a-H,4,7,8,9), 1.22 (t, J = 7.1 Hz, 3 H, OCH_2CH_3), 0.89 (s, 3 H, 9b-methyl) ppm. ^{13}C NMR ($CDCl_3$, 50 MHz): δ = 131.67 (C-6), 127.46 (C-5), 102.09 (C-2), 79.89 (C-9a), 71.21 (C-6a), 63.85 (OCH_2CH_3), 37.20 (C-3a), 36.74 (C-4), 35.92 (C-9b), 33.17 (C-3), 29.00 (C-7), 25.55 (C-9), 22.52 (C-9b methyl), 16.33 (C-8), 15.02 (OCH_2CH_3) ppm. MS: m/z (%) = 252 (13) [M$^+$], 235 (14), 189 (72), 145 (100), 105 (78), 91 (95), 79 (78). HRMS: calcd. for $C_{15}H_{24}O_3$ 252.1725; found, 252.1725.

Ketone 9: A solution of the alcohol **8** (65 mg; 0.32 mmol) in anhydrous CH_2Cl_2 (3 mL) was bubbled with an argon flow to displace the oxygen. The solution was protected from light and maintained under argon. PCC supported on neutral alumina (800 mg) was added to the mixture, which was then stirred at room temperature for 3 h. When the reaction was complete (TLC), the mixture was filtered under vacuum through Celite and a silica gel pad, washed three times with CH_2Cl_2, and dried with anhydrous sodium sulfate, and the solvents were evaporated. The crude product, purified by column chromatography, yielded **9** (70.5 mg; 92%) as a white solid. **9a (*α*-acetal):** M.p. (from diisopropyl ether): 145−146 °C. ^{1}H NMR ($CDCl_3$, 200 MHz): δ = 5.83 (br. s, 1 H, 6-H), 4.80 (d, J = 3.3 Hz, 1 H, 2-H), 3.81 (t, J = 3 Hz, 1 H, 9a-H), 3.67 (dq, J_1 = 14.2 and J_2 = 7.1 Hz, 1 H, OCH_2CH_3), 3.44 (dq, J_1 = 14.2 and J_2 = 7.1 Hz, 1 H, OCH_2CH_3), 2.79 (dd, B part of ABX system, J_1 = 18.0 and J_2 = 5.2 Hz, 1 H, 4-H), 2.50−1.50 (m, 8 H, 3a-H, 4-H, 7-H, 8-H, 9-H), 1.76 (dd, J_1 = 13.4 and J_2 = 3.4 Hz, 1 H, 3-H), 1.53 (ddd, J_1 = 13.6, J_2 = 4.8 and J_3 = 1.2 Hz, 1 H, 3-H), 1.31 (s, 3 H, 9b-methyl), 1.22 (t, J = 7 Hz, 3 H, OCH_2CH_3) ppm. ^{13}C NMR ($CDCl_3$, 50 MHz): δ = 198.14 (C-5), 165.88 (C-6a), 125.64 (C-6), 96.32 (C-2), 70.66 (C-9a), 62.40 (OCH_2CH_3), 39.89 (C-4), 38.45 (C-9b), 34.72 (C-3a), 32.13 (C-9), 31.85 (C-7), 26.86 (C-3), 22.73 (C-9b methyl), 20.05 (C-8), 15.02 (OCH_2CH_3) ppm. **9b (*β*-acetal):** M.p. (from diisopropyl ether) 138−139 °C. IR (KBr): $\tilde{\nu}$ = 2915, 1680, 1620, 1430, 1240, 1140, 1060, 1030, 980, 950 cm^{-1}. ^{1}H NMR ($CDCl_3$, 200 MHz): δ = 5.82 (br. s, 1 H, 6-H), 4.50 (dd, J_1 = 10.6 and J_2 = 2.9 Hz, 1 H, 2-H), 3.81 (m, 1 H, OCH_2CH_3), 3.50 (m, 1 H, OCH_2CH_3), 3.47 (d, J = 3 Hz, 1 H, 9a-H), 2.80 (dd, 1 H, B part of ABX system, J = 18.0, 5.0 Hz, 4-Hβ), 2.50−1.50 (m, 10 H), 1.28 (s, 3 H, 9b-methyl), 1.22 (t, J = 7 Hz, 3 H, OCH_2CH_3) ppm. ^{13}C NMR ($CDCl_3$, 50 MHz): δ = 197.68 (C-5), 165.79 (C-6a), 125.66 (C-6), 101.04 (C-2), 78.88 (C-9a), 63.78 (OCH_2CH_3), 39.98 (C-3a), 39.98 (C-4), 38.31 (C-9b), 33.85 (C-7), 31.74 (C-9), 26.95 (C-3), 22.12 (C-9b methyl), 19.77 (C-8), 15.01 (OCH_2CH_3) ppm. $C_{15}H_{22}O_3$ (250.33): calcd. C 71.95, H 8.86; found C 71.67, H 8.82.

Oxo Acid 5a: Water (0.075 mL), CCl_4 (0.5 mL), sodium periodate (62 mg; 0.3 mmol) and finally hydrated ruthenium oxide (2 mg), were added to the enone **9** (17.5 mg; 0.07 mmol), dissolved in acetonitrile (0.5 mL). The reaction mixture was stirred at room temperature. Two additional portions of sodium periodate (62 mg; 0.3 mmol each) were added 6 h apart, and finally the mixture was left standing overnight. Brine was added and the aqueous layer was extracted with Et_2O (6 × 5 mL). The combined organic extracts were dried with anhydrous sodium sulfate and the solvents were evaporated. Purification by column chromatography yielded **5a** (18.4 mg; quantitative yield) as a colorless oil. IR ($CHCl_3$): $\tilde{\nu}$ = 3200, 1720, 1715, 1420, 1275, 1100, 1040, 920 cm^{-1}. ^{1}H NMR ($CDCl_3$, 200 MHz): δ = 4.81 (d, J = 3.2 Hz, 1 H, 2-H), 4.06 (br. s, 1 H, 8a-H), 3.60 (d quadruplet, A part of ABX_3 system, J_{AX} = 7.0 and J_{AB} = 10.4 Hz, 1 H, OCH_2CH_3,), 3.46 (d quadruplet, B part of ABX_3 system, J = 7.0, 10.4 Hz, 1 H, OCH_2CH_3), 2.70 (m, 4 H, 6-H and 4-H), 2.21−2.09 (m, 8 H, 3-H, 4-H, 7-H, 8-H), 1.24 (s, 3 H, 4a-methyl), 1.20 (t, J = 7 Hz, 3 H, OCH_2CH_3) ppm. ^{13}C NMR ($CDCl_3$, 50 MHz): δ = 214.22 (C-5), 179.13 (COOH), 96.87 (C-2), 75.30 (C-8a), 62.48 (OCH_2CH_3), 50.68 (C-4a), 38.77 (C-6), 35.51 (C-4), 35.38 (C-4), 32.68 (C-8), 26.09 (C-3), 21.81 (C-7), 20.72 (C-4a methyl), 14.97 (OCH_2CH_3) ppm. $C_{14}H_{22}O_5$ (270.32): calcd. C 62.20, H 8.20; found C 62.14, H 8.21.

Note: The same procedure was used for the direct preparation of **5a** from **8**. The oily product was obtained in quantitative yield and the spectroscopic data are identical to those obtained from **9**.

Bis(acetal) 10: Solid $NaHCO_3$ (111 mg), followed by H_2O_2 (30%, 0.96 mL), was added to a solution of selenyl bis(acetal) **2b** (200 mg; 0.54 mmol) in THF (12 mL). The reaction mixture was stirred at room temperature for 2 h, and was then treated with brine (5 mL) and extracted with Et_2O (3 × 10 mL). The combined organic extracts were dried with sodium sulfate and the solvent was removed under reduced pressure. The residue was purified by column chromatography (4% EtOAc/hexanes) to provide **10** (102 mg; 92%) as a white solid; m.p. 36−37.28 °C. IR (KBr): $\tilde{\nu}$ = 3060, 2985, 1650, 1460, 1328, 1275, 1165, 1125, 1080, 1050, 995, 740 cm^{-1}. ^{1}H NMR ($CDCl_3$, 200 MHz): δ = 5.73 (ddd, J_1 = 9.81, J_2 = 3.4 and J_3 = 0.2 Hz, 1 H, 6-H), 5.58 (br. d, J = 9.8 Hz, 1 H, 5-H), 4.96 (t, 1 H, 2-H), 3.76 (t, 1 H, 9a-H), 2.32 (m, 2 H, 4-H), 1.65−1.50 (m, 9 H, 3-H, 3a-H, 7-H, 8-H, 9-H), 0.87 (s, 3 H, 9b-H methyl) ppm. ^{13}C NMR ($CDCl_3$, 50 MHz): δ = 132.02 (C-5), 126.44 (C-6), 87.43 (C-2), 75.69 (C-9a), 71.71 (C-6a), 36.84 (C-3), 31.20 (C-3a), 31.12 (C-9b), 30.93 (C-7), 30.55 (C-4), 26.33 (C-9), 17.23 (C-9b-methyl), 15.87 (C-8) ppm. MS: *m*/*z* (%) = 206 (13) [M$^+$], 160 (42), 145 (51), 131 (22), 117 (27), 105 (37), 91 (100), 77 (31), 65 (20), 55 (33). HRMS: calcd. for $C_{13}H_{18}O_2$ 206.1305; found*,* 206.1306.

Formyl Ester 6: An ozone stream was bubbled at −78°C through a suspension of **10** (50 mg; 0.24 mmol) and $NaHCO_3$ (80 mg; 0.96 mmol) in a 5:1 mixture of CH_2Cl_2/MeOH (2 mL) until complete consumption of olefinic acetal **10** was observed. $NaHCO_3$ was removed by filtration. The filtrate was concentrated in vacuo to give crude **6** as a colorless oil, which was taken up in CH_2Cl_2 (1 mL) and cooled to 0 °C, and Ac_2O (0.11 mL) and Et_3N (0.05 mL) were added. The reaction mixture was stirred at room temperature for 24 h, then extracted with Et_2O and washed with brine. The combined organic extracts were dried (Na_2SO_4) and concentrated under vacuum. The crude product was purified by column chromatography (25% EtOAc/hexanes) to afford **6** (50.9 mg; 78%) as white crystals; m.p. 97−97.58 °C. IR (KBr): $\tilde{\nu}$ = 2980, 2850, 2735, 1740, 1735, 1460, 1328, 1275, 1180, 1100, 1075 cm^{-1}. ^{1}H NMR ($CDCl_3$, 200 MHz): δ = 9.82 (s, 1 H, C*H*O), 5.18 (t, J = 1.2 Hz, 1 H, 2-H), 3.77 (br. s, 1 H, 8a-H), 3.65 (s, 3 H, COOMe), 2.56 (dd, A part of ABX system, J_{AB} = 15.0 and J_{AX} = 3.2 Hz, 1 H, 4-H), 2.49 (ddd, A part of ABCX system, J_{AB} = 14.1, J_{AC} = 10.7 and J_{AX} = 2.8 Hz, 1 H, 3-Hβ or 4-H), 2.30−1.10 (m, 3-H, 4-H, 6-H, 7-H, 8-H), 1.03 (s, 3 H, 4a-H methyl) ppm. ^{13}C NMR ($CDCl_3$, 50 MHz): δ = 205.78 (*C*HO), 172.55 (*C*OOMe), 89.95 (C-2), 82.78 (C-5), 78.61 (C-8a), 51.77 ($COOCH_3$), 38.12 (C-4), 37.27 (C-3), 36.65 (C-4), 36.10 (C-4a), 27.73 (C-6), 26.15 (C-8), 15.38 (CH_3), 14.26 (C-7) ppm. MS: *m*/*z* (%) = 269 (40) [MH$^+$], 239 (25), 207 (100), 165 (90), 147 (13), 121 (15), 111 (37), 59 (22), 55 (50). HRMS: calcd. for $C_{14}H_{21}O_5$ 269.1389; found 269.1388.

Diester 11: Solid sodium hydrogen carbonate (80 mg) was added to a cooled (0°C) solution of ester **6** (100 mg; 0.36 mmol) in 12 mL of CH_2Cl_2, followed in small portions by *m*CPBA (172 mg). After 6 h, the reaction mixture was poured into a saturated solution of sodium chloride (10 mL) and extracted with CH_2Cl_2 (3 × 10 mL). The combined organic extracts were washed with 1 M NaOH and water until neutrality was reached. The organic layer was dried with sodium sulfate and filtered, and the solvent was removed under reduced pressure to give **11** (quantitative yield) as a pale-yellow oil. IR ($CHCl_3$): $\tilde{\nu}$ = 3060, 2850, 1750, 1740, 1450, 1290, 1200, 1175, 980 cm^{-1}. ^{1}H NMR ($CDCl_3$, 200 MHz): δ = 8.46 (s, 1 H, OCHO), 5.19 (br. s, 1 H, 2-H), 3.97 (br. s, 1 H, 8a-H), 3.67 (s, 3 H, COOMe), 2.83 (dd, A part of ABX system, J_1 = 16.3 and J_2 = 3.4 Hz, 1 H, 4-H), 2.62 (d, AB system, J_1 = 10.8 Hz, 1 H, 3-H), 2.49 (dddd, J_1 = J_2 = 12.0, J_3 = 9.8 and J_4 = 2.2 Hz, 1 H, 7-Hβ), 2.30−1.30 (m, 8 H, 3-H, 4-H, 4-H, 6-H, 7-H, 8-H), 1.09 (s, 3 H, 4a-H methyl) ppm. ^{13}C NMR ($CDCl_3$, 50 MHz): δ = 173.42 (*C*O_2Me), 159.86 (CHO), 106.89 (C-5), 91.03 (C-2), 80.16 (C-8a), 51.55 (CO_2CH_3), 37.96 (C-4), 36.53 (C-4a), 36.02 (C-3), 35.19 (C-4), 32.51 (C-6), 25.55 (C-8), 17.17 (C-7), 15.22 (CH_3). MS: *m*/*z* (%) = 178 (25), 165 (20), 95 (100), 82 (38), 67 (60). $C_{14}H_{20}O_6$ (284.30): calcd. C 59.15; H 7.09; found C 59.19, H 7.14.

Lactone 4. Route a: Compound **5a** (61 mg; 0.22 mmol) was dissolved in THF (4 mL), water (2 mL), and HCl (6 N, 0.5 mL), and the mixture was heated at reflux for 12 h. The solution was cooled and 10% $NaHCO_3$ solution was added until neutrality. The aqueous phase was extracted with Et_2O (3 × 5 mL). The combined organic extracts were dried with sodium sulfate and the solvents were evaporated, yielding **5b**. Without purification, a catalytic amount of *p*-toluenesulfonic acid and milled molecular sieves (4 Å) were directly added to a solution of crude **5b** (50 mg; 0.21 mmol) in toluene (12 mL). The mixture was stirred at room temperature for 5 d. The solid was removed by filtration and the filtrate was poured into 10% $NaHCO_3$ solution, extracted with Et_2O (3 × 10 mL), and dried with sodium sulfate, and the solvents were evaporated under reduced pressure. Preparative chromatography of the oily residue (EtOAc/hexanes, 1:1, R_f = 0.4) yielded **4** (33.6 mg; 70%) as a colorless oil. **Route b:** Diester **11** (100 mg; 0.35 mmol) was added to a solution of LiOH·H_2O (73.5 mg; 1.75 mmol) in 10 mL of EtOH, and the mixture was stirred at room temperature for 1 h. The solvent was removed under reduced pressure. The residue was poured into H_2O (1 mL)/Et_2O (3 mL) and then treated with 1 N HCl until pH = 3 was reached. The mixture was extracted with Et_2O (2 × 5 mL) and EtOAc (2 × 5 mL), washed with brine until neutrality, and dried with sodium sulfate. The aqueous layer was extracted with Et_2O (3 × 5 mL), dried, and concentrated under vacuum, giving compound **12** (80 mg; 92%) as colorless oil. Without purification, a solution of **12** (80 mg; 0.32 mmol), DCC (412.66 mg; 0.36 mmol), and DMAP (3.90 mg; 0.032 mmol) in CH_2Cl_2 (2 mL) was allowed to stand at room temperature for 22 h until esterification was complete. *N*,*N*-Dicyclohexylurea was separated by filtration and the filtrate was washed with water (3 × 6 mL), 5% HOAc (3 × 6 mL) and again water (3 × 6 mL), and dried (Na_2SO_4), and the solvents were evaporated in vacuo to afford **4** (60.5 mg; 85%) as a colorless oil. IR ($CHCl_3$): $\tilde{\nu}$ = 2950, 2940, 1745, 1450, 1370, 1218, 1190, 1064, 915, 819 cm^{-1}. ^{1}H NMR ($CDCl_3$, 200 MHz): δ = 5.17 (t, J = 2.2 Hz, 1 H, 5-H), 4.06 (br. s, 1 H, 6a-H), 2.98 (dd, J = 18.3, 6.2 Hz, 1 H, 3-H), 2.53 (dd, J = 18.3, 1.3 Hz, 1 H, 3-H), 2.41 (ddd, A part of ABCX system, J_{AC} = 13.8, J_{AB} = 14.9 and J_{AX} = 2.0 Hz, 1 H, 4-Hα), 2.2−1.3 (m, 8 H, 3a-H, 4-Hβ, 7-H, 8-H, 9-H), 1.16 (s, 3 H, 9b-H methyl) ppm. ^{13}C NMR ($CDCl_3$, 50 MHz): δ = 177.68 (CO), 104.87 (C-9a), 89.60 (C-5), 75.36 (C-6a), 37.45 (C-9b), 37.09 (C-3), 32.08 (C-3a), 30.88 (C-9), 29.98 (C-4), 25.79 (C-7), 16.75 (C-8), 16.59 (C-9b methyl) ppm. MS: *m*/*z* (%) = 225 (59) [MH$^+$], 207 (35), 165 (23), 110 (100), 94 (56), 84 (79), 69 (35), 55 (61). $C_{12}H_{16}O_4$: calcd. C 64.27, H 7.19; found C 64.20, H 7.12.

Supporting Information (see footnote on the first page of this article): ^{1}H and ^{13}C NMR spectra for compounds **4**, **5a**, **6**, **8**, **9**, **10**, **11**.

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[15] The first stages of the synthetic route presented in Scheme 3 were also performed in parallel with α- and β-acetal epoxides **3** to establish the epimers' behavior in each reaction toward the desired products. However, since a definite stereochemistry at the acetal carbon atom in compound **3** did not seem to affect the production of any of its derivatives and would be lost in the hemiacetal formation **5a** → **5b**, we decided to carry out the whole sequence with the epimeric mixture.

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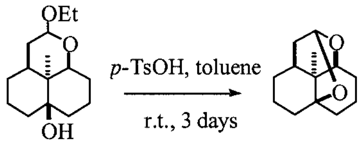
[20] As shown in the following transformation, we have already observed that in tricyclic compounds, the intramolecular *trans*-acetal formation occurs with the axially oriented C-6a hydroxy group.



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