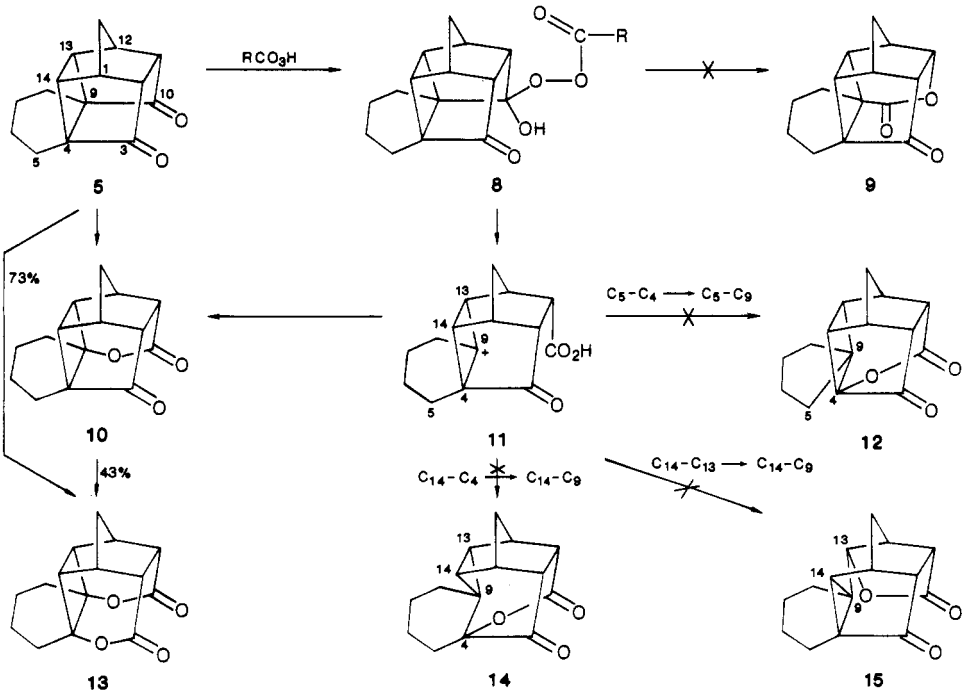
Scheme III



from methanol to give the rearranged lactone **7** (138 mg, 43%). The melting point, IR, ^{1}H NMR, and MS characteristics of **7** were similar to those reported by Mehta and Singh.[9]

Catalytic Hydrogenation of Hexacyclo-[10.2.1.0^{2,11}.0^{4,9}.0^{4,14}.0^{9,13}]pentadeca-5,7-diene-3,10-dione (6). A solution of unsaturated dione **6** (300 mg, 1.33 mmol) in dry methanol (25 mL) was hydrogenated over preactivated platinum dioxide (100 mg) at a hydrogen pressure of 30 psi for 8 h. The reaction mixture was filtered to remove the catalyst, and the filtrate was concentrated in vacuo to give a residue, which was chromatographed over a silica gel column (10 g). The purified material was recrystallized from a minimum amount of methanol to give white crystals of the reduced dione **5** (185 mg, 60%): mp 70 °C; IR (neat) 2900 (s), 2840 (s), 1740 (s), 1720 (s), 1450 (m), 1440 (m), 1370 (w), 1100 (m) cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.05–2.20 (m, 10 H), 2.75 (s, 2 H), 2.85 (s, 4 H); ^{13}C NMR ($CDCl_3$) δ 213.297 (s), 55.046 (d), 49.587 (s), 44.193 (d), 43.543 (d), 41.073 (t), 22.616 (t), 19.172 (t); mass spectrum *m/e* (relative intensity) 228 (100) M$^+$, 200 (23), 135 (27), 129 (29), 107 (34), 91 (44), 77 (40), 66 (33). Anal. Calcd for $C_{15}H_{16}O_2$: C, 78.94; H, 7.01. Found: C, 78.76; H, 7.12.

Baeyer–Villiger Oxidation of Hexacyclo-[10.2.1.0^{2,11}.0^{4,9}.0^{4,14}.0^{9,13}]pentadeca-3,10-dione (5). (i) With 2.5 equiv of *m*-Chloroperbenzoic Acid. To a solution of dione **5** (290 mg, 1.27 mmol) in dry benzene (20 mL) were added *m*-chloroperbenzoic acid (540 mg, 3.17 mmol) and *p*-toluenesulfonic acid (10 mg). The mixture was stirred at room temperature for 8 h, poured into water (20 mL), and extracted with ether (3 × 20 mL). The combined organic extracts were washed with aqueous sodium bicarbonate (2 × 10 mL) and brine (10 mL) and dried over anhydrous sodium sulfate. Evaporation of the solvent gave a product mixture, which was separated by silica gel column chromatography. Elution with acetone–petroleum ether (15:85) gave a white solid, which was recrystallized from methanol to give monolactone **10** (160 mg, 51%): mp 93 °C; IR ($CHCl_3$) 2920 (s), 2840 (s), 1760–1740 (br s), 1450 (m), 1300 (s), 1050 (s), 750 (s) cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.05–2.2 (br m, 10 H), 2.35–3.19 (m, 6 H); ^{13}C NMR ($CDCl_3$) δ 213.232 (s), 172.743 (s), 78.053 (s), 57.841 (s), 52.317 (d), 47.637 (d), 43.218 (d), 42.828 (d), 41.268 (d), 39.708 (d), 39.579 (t), 32.560 (t), 20.796 (t), 17.677 (t), 16.962 (t); mass spectrum *m/e* (relative intensity) 244 (40) M$^+$, 216 (43), 179 (44), 151 (49), 122 (72), 91 (100), 66 (90). Anal. Calcd for $C_{15}H_{16}O_3$: C, 73.77; H, 6.55. Found: C, 73.43; H, 6.69.

Further elution with the above solvent mixture gave the dilactone **13** (120 mg, 36%, after recrystallization from methanol): mp 160 °C; IR (Nujol) 2920 (s), 2840 (s), 1750 (s), 1460 (s), 1330 (s), 1180 (s), 1070 (s), 790 (w); ^{1}H NMR ($CDCl_3$) δ 1.1–2.1 (m, 10 H), 2.72 (br s, 2 H), 2.81 (s, 2 H), 3.20 (s, 2 H); ^{13}C NMR ($CDCl_3$ 270 MHz) δ 169.993 (s), 82.482 (s), 44.603 (d), 40.260 (d), 40.265 (d), 39.159 (t), 30.289 (t), 14.688 (t); mass spectrum *m/e* (relative intensity) 260 (20) M$^+$, 161 (50), 117 (32), 100 (26), 91 (100), 79 (26), 66 (51), 55 (30). Anal. Calcd for $C_{15}H_{16}O_4$: C, 69.23; H, 6.15. Found: C, 69.63; H, 6.69.

(ii) With 5 equiv of *m*-Chloroperbenzoic Acid. Exhaustive B–V oxidation of dione **5** (300 mg, 1.33 mmol) with *m*-chloroperbenzoic acid (1.13 g, 6.65 mmol) and catalytic *p*-toluenesulfonic acid was carried out by stirring in benzene (20 mL) for 8 h. The usual workup and purification as above gave **13**, 250 mg (73%).

Baeyer–Villiger Oxidation of Monolactone 10. To a solution of monolactone (100 mg, 0.4 mmol) in dry benzene (10 mL) were added *m*-chloroperbenzoic acid (180 mg, 1.09 mmol) and catalytic *p*-toluenesulfonic acid (10 mg), and the reaction mixture was stirred for 4 h. The usual workup and purification as above gave 52 mg (48%) of dilactone **13**.

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Registry No. **5**, 33741-25-2; **6**, 24402-96-8; **7**, 70157-07-2; **10**, 120231-22-3; **13**, 120231-21-2.

Oxidation of Diols with Alkali Hypochlorites Catalyzed by Oxammonium Salts under Two-Phase Conditions

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Several procedures for the oxidation of alcohols to carbonyl derivatives mediated by oxammonium salts have been described.[1] We recently reported a catalytic cycle

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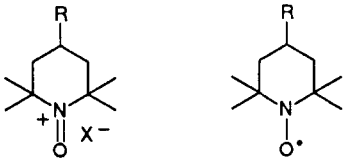
Table I. Oxidation of Diols

entry	diol	procedure[a,b]	catalyst	product	isolated yield, %
1	PhCH(OH)CH(OH)Ph	A (1.1)	**2a**	PhC(O)CH(OH)Ph	85
2	PhCH(OH)CH(OH)Ph	A (2.4)	**2a**	PhC(O)C(O)Ph	97
3	1,4-$(OH)_2C_6H_4$	A (2.4)	**2a**	1,4-$(=O)_2C_6H_4$	95
4	$CH_3CH(OH)(CH_2)_8CH_2OH$	A (1.1)	**2b**	$CH_3CH(OH)(CH_2)_8CHO$	68[c]
5	$CH_3CH(OH)(CH_2)_8CH_2OH$	A (2.2)	**2b**	$CH_3CO(CH_2)_8CHO$	69[d]
6	$CH_3CH(OH)(CH_2)_8CH_2OH$	A (3.6)[e]	**2b**	$CH_3CO(CH_2)_8COOH$	57[f]
7	$HOCH_2(CH_2)_2CH_2OH$	B (2.4)	**2a**	$\overline{C(O)CH_2CH_2CH_2O}$	69
8	$HOCH_2(CH_2)_3CH_2OH$	B (2.4)	**2b**	$\overline{C(O)CH_2CH_2CH_2CH_2O}$	58
9	$HOCH_2CH_2N(Ts)CH_2CH_2OH$	A (2.4)	**2b**	$\overline{C(O)CH_2N(Ts)CH_2CH_2O}$	85

[a] Reactions were performed on a 15–24-mmol scale. A: CH_2Cl_2–0.9 M aqueous NaOCl at pH 9.5, 0.01 molar equiv of **2a** (or **2b**) and 0.1 molar equiv of KBr. B: CH_2Cl_2–solid LiOCl, 3.0 molar equiv of $NaHCO_3$ and 0.01 molar equiv of **2a** (or **2b**). [b] Molar equivalent of hypochlorite ion/substrate in parentheses. [c] 10-Oxoundecanal (10%) was also isolated. [d] 10-Oxoundecanoic acid (14%) was also isolated. [e] In the presence of 0.05 molar equiv of Aliquat 336. [f] No main side products were isolated.

in which oxammonium salt **1a** is continuously regenerated from nitroxyl radical **2a** under CH_2Cl_2–aqueous NaOCl two-phase conditions.[2]

In the present paper we describe the extension of this methodology to the selective oxidation of diols.



1 **2**

a, R = OCH_3
b, R = H

Oxidations were carried out in CH_2Cl_2–aqueous NaOCl at 10–15 °C and pH 9.5[3] in the presence of 0.01 molar equiv of the commercially available radical **2b** and 0.10 molar equiv of KBr. 1,2-Diphenyl-1,2-ethanediol affords benzoin or benzil in 85 and 97% yield, respectively, depending on the amount of aqueous NaOCl used (Table I, entries 1,2). Hydroquinone is easily oxidized to 1,4-benzoquinone in almost quantitative yield (entry 3).

Selective oxidation of diols containing both primary and secondary hydroxyl groups is particularly attractive. Indeed we had found appreciable differences in the oxidation rates of primary vs secondary alcohols.[2] 1,10-Undecanediol (chosen as model substrate) is converted into 10-hydroxyundecanal or 10-oxoundecanal in 68 and 69% isolated yields by using 1.1 and 2.2 molar equiv of oxidant, respectively (entries 4, 5). The main side products are 10-oxoundecanal (10%) and 10-oxoundecanoic acid (14%) in the two cases, respectively. Oxidation with 3.6 molar equiv of oxidant and 0.05 molar equiv of trioctylmethylammonium chloride (Aliquat 336) as phase-transfer catalyst affords 10-oxoundecanoic acid, readily isolated from the reaction mixture in 57% yield (entry 6).

Lactones are the preferred products starting from diols in which the two hydroxyl functions are in 1,4- or 1,5-positions on a flexible chain. Thus 1,4-butanediol and 1,5-pentanediol afford γ-butyrolactone and δ-valerolactone, respectively, in fairly good yields (entries 7, 8). Lactonization also occurs with substrates containing heteroatoms: e.g. *N*,*N*-bis(2-hydroxyethyl)-*p*-toluenesulfonamide is converted into *N*-tosylmorpholinone (entry 9). Unfortunately oxidation of α,ω-diols that cannot form five- or six-membered lactones gives unresolvable mixtures of polymeric products.

Our results with 1,4-butanediol and 1,5-pentanediol are comparable to those obtained by Endo et al. using stoichiometric amounts of oxammonium salts.[8] As already reported, lactonization likely occurs via oxidation of the cyclic hemiacetal of the ω-hydroxy aldehyde.[1d,8]

1,4-Butanediol and 1,5-pentanediol are very hydrophilic and are more conveniently oxidized under solid–liquid two-phase conditions (LiOCl–CH_2Cl_2) in the presence of $NaHCO_3$ and 0.01 molar equiv of **2a** or **2b**. Reactions are over in less than 30 min. Commercial solid LiOCl contains 7% of water (1.9 mol of water/mol of hydroxyl function), so that the reaction conditions can be assimilated to those of a *pseudo* solid–liquid system.[9] Without $NaHCO_3$ reaction rates are much slower. The importance of "buffering agent" in the reaction mixture is very likely related to a mechanism via HOCl,[2] which is the effective oxidizing species and is readily extracted in the organic phase. Accordingly the presence of a phase-transfer catalyst is not required.

It must be pointed out that the procedure with LiOCl also proved to be efficient for the oxidation of hydrophilic alcohols to carbonyl derivatives, e.g. 1-butanol is converted into butanal in 80% yield in 20 min at 0 °C.

Experimental Section

2,2,6,6-Tetramethylpiperidine-1-oxyl was purchased from Janssen Chimica, Beerse, Belgium. 4-Methoxy-2,2,6,6-tetramethylpiperidine-1-oxyl[10] and *N*,*N*-bis(2-hydroxyethyl)-*p*-toluenesulfonamide[11] were prepared according to known procedures.

Aqueous NaOCl was prepared by diluting to 0.9 M a fresh technical grade sample (15–17% of active chlorine; pH 12.7) and,

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(3) Concentrations of aqueous NaOCl in the range 0.3–2.0 M can be used. The pH of the aqueous phase is adjusted to a value in the range 8.6–9.5 by addition of solid $NaHCO_3$.

(4) Few methods for the oxidation of primary hydroxyl functions of primary–secondary diols have been reported so far (among others with nickel alkanoates–Br_2[5] and tris(triphenylphosphine)ruthenium chloride[6]). Aldehydes containing a secondary hydroxyl group can be also prepared by selective reduction of the corresponding keto aldehydes.[7]

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immediately before use, adjusting the pH at 9.5 with 17 g/L of $NaHCO_3$. LiOCl was purchased from Fluka AG, Buchs, Switzerland. The commercial solid should contain 30% of LiOCl. Repeated iodometric titrations of the batch used in this work showed an oxidant content of 19.6–20.5% as LiOCl.

Oxidations with Aqueous Sodium Hypochlorite. The reaction flask was charged with 15 mmol of substrate, 0.15 mmol of **2a** (or **2b**), 1.5 mmol of KBr, 50 mL of CH_2Cl_2, and 2 mL of H_2O and stirred. The appropriate amount of a 0.9 M solution of NaOCl at pH 9.5 (see Table I) was added in 5–10 min, maintaining the temperature in the range 10–15 °C with an ice bath. After 10 min the organic phase was separated and washed with 10 mL of 10% HCl containing 125 mg (0.75 mmol) of KI, 10 mL of 10% aqueous $Na_2S_2O_3$, and 10 mL of H_2O. After drying ($MgSO_4$) and evaporation of the solvent, the residue was purified by column chromatography on silica gel. All of the isolated products showed physical and spectroscopic (IR, ^1H NMR) properties in agreement with previously reported data. Results are shown in Table I. For the oxidation of 1,10-undecanediol to 10-oxoundecancarboxylic acid (Table I, entry 6), the addition of 0.75 mmol of Aliquat 336 was required.

Oxidative Lactonization of 1,4-Butanediol and 1,5-Pentanediol. A mixture of 24 mmol of diol, 0.24 mmol of **2a** (or **2b**), 16.8 g (57.6 mmol) of 20% LiOCl, and 6.05 g (72 mmol) of $NaHCO_3$ in 50 mL of CH_2Cl_2 was vigorously stirred at room temperature over 30 min. The reaction mixture was filtered, and the solid was thoroughly washed with CH_2Cl_2. After drying ($MgSO_4$) and evaporation of the solvent, the residue was purified by column chromatography (silica gel; petroleum ether–Et_2O). The products showed physical and spectroscopic properties identical with those reported for γ-butyrolactone and γ-valerolactone.

Registry No. **2a**, 95407-69-5; **2b**, 2564-83-2; PhCH(OH)CH(OH)Ph, 492-70-6; 1,4-$(OH)_2C_6H_4$, 123-31-9; $CH_3CH(OH)(CH_2)_8CH_2OH$, 10596-05-1; $HO(CH_2)_4OH$, 110-63-4; $HO(CH_2)_5OH$, 111-29-5; $HO(CH_2)_2N(Ts)(CH_2)_2OH$, 7146-67-0; PhC(O)CH(OH)Ph, 119-53-9; PhC(O)C(O)Ph, 134-81-6; 1,4-$(=O)_2C_6H_4$, 106-51-4; $CH_3CH(OH)(CH_2)_8CHO$, 38199-58-5; $CH_3C(O)(CH_2)_8CHO$, 36219-78-0; $\overline{C(O)CH_2CH_2CH_2O}$, 96-48-0; $\overline{C(O)CH_2CH_2CH_2CH_2O}$, 542-28-9; $\overline{CnO)CH_2N(Ts)CH_2CH_2O}$, 91134-36-0; NaOCl, 7681-52-9; LiOCl, 13840-33-0; 10-oxoundecanoic acid, 676-00-6.

Regioselective Acylations of 7-Desacetylforskolin[1]

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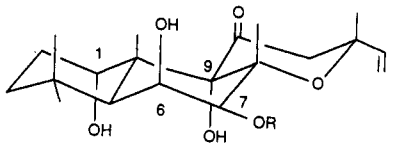
Forskolin (**1a**) is a diterpenoid, isolated from the roots of *Coleus forskohlii*.[2] Several total syntheses of forskolin have recently been reported.[3] During the course of an investigation of the physiological effects of forskolin analogues, it was of interest to prepare 1-esters (axial) and 7-esters (equatorial) of 7-desacetylforskolin (7-DAF, **1b**). It is known from the work of Eliel[4] and others[5] that equatorial alcohols are more reactive with respect to acylation than their axial counterparts. Consistent with these



1a R = $COCH_3$

1b R = H

observations is the report[6] that treatment of 7-DAF (**1b**) with propionic anhydride in pyridine provides predominately the 7-ester, the product of acylation of the equatorial 7-hydroxyl group rather than acylation of the axial 1-hydroxyl group.[7]

We found, however, that treatment of 7-DAF (**1b**) with bromoacetyl bromide and dimethylaniline in dichloromethane at 0–5 °C effected acylation exclusively on the *axial* 1-hydroxyl to provide, after treatment with morpholine, the 1-(amino ester) **2** in 73% yield (Scheme I). In contrast, treatment of **1b** with 4-morpholinoacetic acid[8] in the presence of DCC and 4-(dimethylamino)pyridine (DMAP)[9] (Scheme I) effected predominately acylation on the equatorial 7-hydroxyl to provide the 7-(morpholinoacetyl ester) **3** in 45% yield (64% based on recovered **1b**) in addition to 10% of the 1-(morpholinoacetyl ester) **2** and 15% of 7-desacetyl-1,7-bis(morpholinoacetyl)forskolin (**4**).

To confirm the structure of compound **2**, it was acylated with acetic anhydride/DMAP to provide 1-(morpholinoacetyl)forskolin (**5**) (Scheme II), which was identical by mp, IR, ^1H NMR, and MS with the product obtained by treating forskolin with bromoacetyl bromide/dimethylaniline, followed by morpholine (Scheme II).

The structure of **3** was confirmed by an independent synthesis employing a 1-hydroxyl-protected forskolin derivative. Seamon et al.[2] had prepared some forskolin analogues in which the 1-hydroxyl was protected as the 1-(*tert*-butyldimethylsilyl ether). However, the conditions required to cleave the *tert*-butyldimethylsilyl ether (fluoride or HF) are not compatible with some of the amino esters that comprised our targets. We chose, therefore, to protect the 1-hydroxyl as a 1,9-dimethylformamide (DMF) acetal[10,11] (Scheme III). Although DMF acetals of 1,2-diols have long been known[10] and 2-(dimethylamino)benzylidene and 1-(dimethylamino)ethylidene acetals have been used to protect sugars,[11] to our knowledge, the somewhat more stable DMF acetals have not been previously employed to protect 1,3-diols in rigid systems.[12] We found that treatment of forskolin (**1a**) with DMF dimethyl acetal provided forskolin-1,9–DMF acetal (**6**), the acetyl group of which was hydrolyzed with aqueous methanolic potassium carbonate to provide the 7-desacetylforskolin-1,9–DMF acetal (**7**) in 74% overall yield from forskolin.[13]

(1) Dedicated to Professor Hansgeorg Gareis on the occasion of his 60th birthday.

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(13) The yield of 7-DAF-1,9–DMF acetal, **7**, was slightly higher if **6** was not isolated.

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