Photoinduced Transformations. 77.[1] A Four-Step Substitution of a Carbonyl Group of Steroidal Ketones by an Oxygen Atom. A New Method for the Synthesis of Cyclic Ethers[2]

Hiroshi Suginome* and Shinji Yamada

Organic Synthesis Division, Department of Chemical Process Engineering, Faculty of Engineering, Hokkaido University, Sapporo 060, Japan

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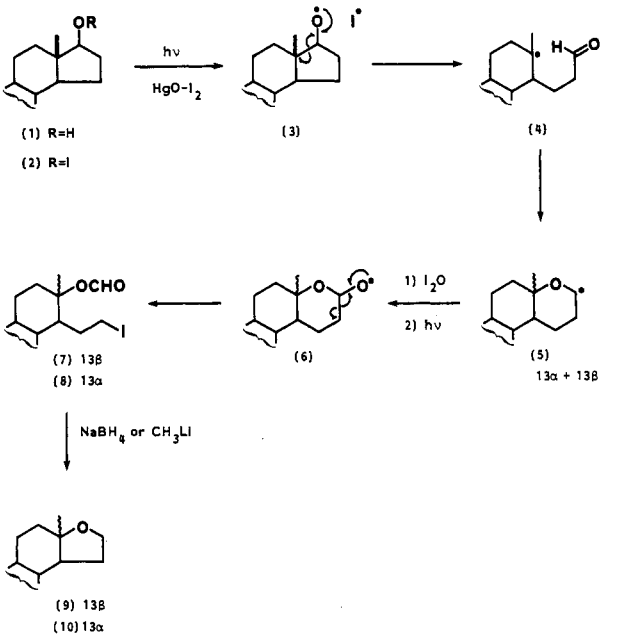
We set out to describe a new and versatile method for transforming steroidal five- and six-membered cyclic ketones as starting materials into steroidal cyclic ethers with the same ring size via four steps; Baeyer–Villiger oxidation of a steroidal ketone to a lactone followed by its reduction with DIBAL gives the corresponding lactol. The irradiation of the hypoiodite generated in situ by means of the reaction of the lactol by an excess of mercury(II) oxide–iodine and pyridine in benzene gives formates arising from a regiospecific β-scission of the C–C bond. These formates can readily be transformed into oxasteroids by treatment with a complex metal hydride or methyllithium. By this new method a variety of steroidal cyclic ketones were transformed into the corresponding cyclic ethers in good overall yields. The stereochemical integrity of the chiral center adjacent to the carbonyl group of the starting cyclic ketones is maintained throughout this transformation.

A survey of the literature indicates that only a limited number of methods for the synthesis of oxasteroids have been available.[3,4] A simple and general method for the synthesis of these important groups of steroids is therefore required.

In our previous publications in this series we reported on the two-step transformation of saturated hydroxy steroids into oxasteroids,[5,6] with an oxygen-containing ring of the same size as that of the starting ring. The method is exemplified by the conversion of 5α-androstan-17β-ol (**1**) into the corresponding oxasteroids **9** and **10** (Scheme I); the irradiation of the hypoiodite **2** generated in situ in the reaction of 5α-androstan-17β-ol (**1**) with an excess of mercury(II) oxide and iodine gives novel formates **7** and **8** arising from the successive reactions triggered by a β-scission of the corresponding alkoxy radical **3** as outlined. These formates can readily be converted into oxasteroids **9** and **10** by treatment with a complex metal hydride or methyllithium. The experiments which use ^{18}O-labeled mercury(II) oxide as a source of $I_2{}^{18}O$ provided evidence that the oxygen atom in the oxasteroids **9** and **10** is derived from the hydroxy group of the starting alcohol **1** and not from the oxygen of mercury(II) oxide.[5] This suggests that

Scheme I



the pathway of the formation of formates **7** and **8** involves β-scission of secondary alkoxyl radical **6** generated from hypoiodites of lactol intermediates. However, the scope of this method for transforming cyclic alcohols into cyclic ethers has been limited since it is only applicable to cyclic alcohols, the alkoxyl radicals generated from which are susceptible to β-scission. For example, it is not applicable to the replacement of the hydroxymethylene group of 5α-cholestan-3β-ol by an oxygen atom to produce 3-oxa-5α-cholestane since the alkoxy radical generated from 5α-cholestan-3β-ol does not undergo β-scission.

In this paper, we report an alternative and considerably more versatile new method for transforming steroidal five- and six-membered cyclic ketones as starting materials into steroidal cyclic ethers with the same ring size via four steps. The method is an extention of our previous study[6] and is applicable not only to the synthesis of oxasteroids but also to the synthesis of cyclic ethers in general.

In our previous paper we showed that the reaction path for the formation of the formates from cyclic alcohols clarified by the ^{18}O-labeling involves the second hypoiodite derived from the lactols as the intermediates (Scheme I).[6]

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(2) Preliminary communication: Suginome, H.; Yamada, S. *Tetrahedron Lett.* **1984**, *25*, 3995–3998.

(3) 1-Oxasteroids, ref 6. 2-Oxasteroids. (a) Kashman, Y.; Kaufman, C. D. *Tetrahedron* **1971**, *27*, 3437–3445. (b) Zanati, G.; Wolff, M. E. *J. Med. Chem.* **1971**, *14*, 958–963. 3-Oxasteroids, ref 6. (c) Suginome, H.; Furusaki, A.; Kato, K.; Maeda, N.; Yonebayashi, F. *J. Chem. Soc., Perkin Trans. 1* **1981**, 236. 4-Oxasteroids, ref 11–14. (d) Dias, J. R.; Pettit, G. R. *J. Org. Chem.* **1971**, *23*, 3485. 6-Oxasteroids. (e) Jacobs, T. L.; Brownfield, R. B. *J. Am. Chem. Soc.* **1960**, *82*, 4033. (f) Speckamp, W. N.; Kesselaar, H. *Tetrahedron Lett.* **1974**, 3405–3408. 7-Oxasteroids. (g) Guthrie, R. W.; Boris, A.; Mullin, J. G.; Mennona, F. A.; Kierstead, R. W. *J. Med. Chem.* **1973**, *16*, 257–262. (h) Guthrie, R. W.; Kierstead, R. W.; Le Mahieu, R. A. U.S. Pat. 3 769 467; *Chem. Abstr.* **1975**, *83*, 43609. (i) Suginome, H.; Shea, C. M. *Bull. Chem. Soc. Jpn.* **1980**, 3387–3388. 11-Oxasteroids. (j) Engel, C. R.; Rastogi, R. C.; Chowdhury, M. N. R. *Steroids* **1972**, *19*, 1–24. (k) Salvi, V. S.; Mukherjee, D.; Chowdhury, M. N. R.; Engel, C. R. *Steroids* **1976**, 717–725. 15-Oxasteroids. (l) Rosen, P.; Boris, A.; Oliva, C. *J. Med. Chem.* **1980**, *23*, 329–340. 16-Oxasteroids. (m) Terasawa, T.; Okada, T. *J. Chem. Soc., Perkin Trans. 1* **1978**, 576–584. 17-Oxasteroids, ref. 6. (n) Rakhit, S.; Gut, M. *J. Org. Chem.* **1964**, *29*, 229–231.

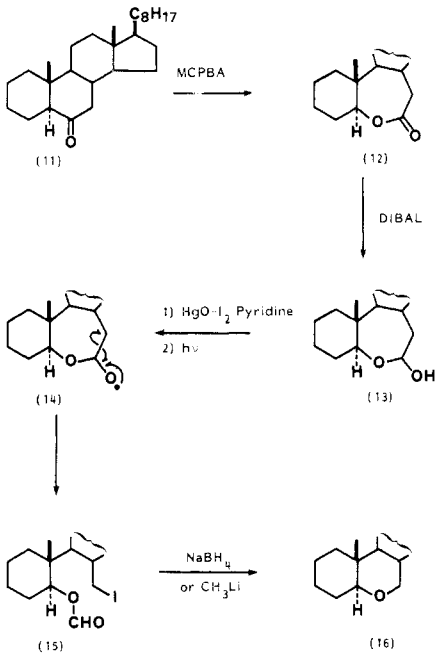
(4) For reviews, see: (a) Morand, P. F.; Lyall, J. *Chem. Rev.* **1968**, *68*, 85–124; (b) Huisman, H. O.; Speckamp, W. N. In "Steroids", International Review of Science, Organic Chemistry; Johns, W. F., Ed.; Butterworths: London, 1976; Series Two, Vol. 8, pp 207–236.

(5) Suginome, H.; Yamada, S.; Miyaura, N. *Chem. Lett.* **1983**, 55.

(6) Suginome, H.; Yamada, S. *J. Org. Chem.* **1984**, *49*, 3753.

0022-3263/85/1950-2489$01.50/0

Scheme II



The lactols are species that are quite readily obtainable from cyclic ketones by the standard method. We reasoned therefore that the irradiation of these lactols in benzene containing a mercury(II) oxide–iodine reagent may give rise to the formates that are generated from the regioselective fission of the C–C bond via the alkoxy radicals (e.g., **6**).

We found this to be the case. Scheme II outlines the conversion of 5α-cholestan-6-one (**11**) into a formate (**15**) and its transformation into 6-oxa-5α-cholestane (**16**) as the first example of this method.

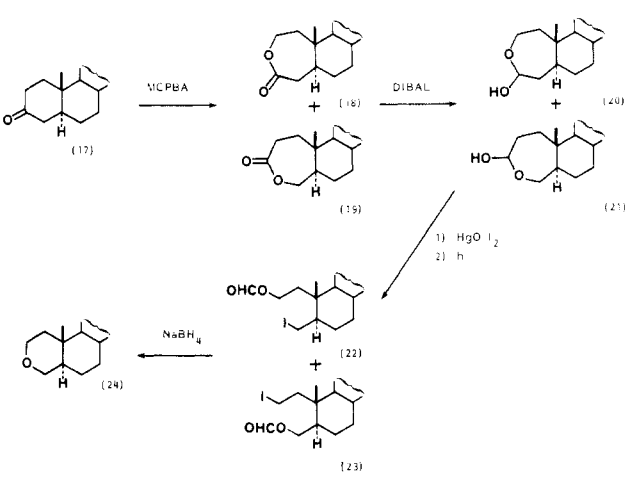
Thus, Baeyer–Villiger oxidation of ketone **11** gave *B*-homo-6-oxa-5α-cholestan-7-one (**12**)[7] in a 57% yield. The reduction of lactone **12** with DIBAL[8] in hexane at −78 °C for 2 h readily gave a crystalline lactol **13**[9] in a 96% yield. Lactol **13** in benzene containing mercury(II) oxide–iodine and pyridine (0.7 mL) in a Pyrex vessel was irradiated with a 100-W high-pressure mercury arc for 3 h under a nitrogen atmosphere to give an oily 6-iodo-5,6-seco-*B*-nor-5α-cholestan-5β-ol formate (**15**) in a 90% yield. The addition of a small amount of pyridine in this photolysis was found to be essential. In the absence of pyridine the lactol in benzene is decomposed by the addition of mercury(II) oxide and iodine. The heating of **15** in THF containing $NaBH_4$ under reflux for 10 h gave crystalline 6-oxa-5α-cholestane (**16**) in a 75% yield.

Prior to our work, Jacobs and Brownfield[9] in 1960 reported the synthesis of an oily 6-oxacholestane with unspecified configuration at the 5-position via eight steps, starting from cholesterol. Nothing analytical nor any physical constants except some infrared data, however, were reported by them.

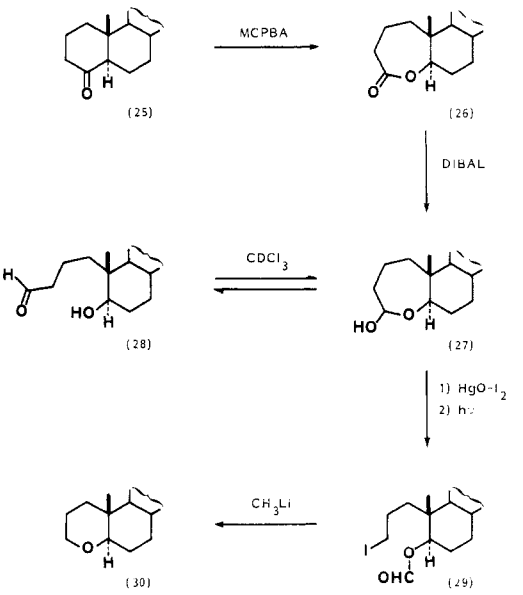
The results of the transformation of other various steroidal ketones into the corresponding cyclic ethers via the corresponding lactols are described below.

3-Oxa-5α-cholestane (24) (Scheme III). Baeyer–Villiger oxidation of 5α-cholestan-3-one (**17**) with *m*-chloroperbenzoic acid (MCPBA) in dichloromethane gave

Scheme III



Scheme IV

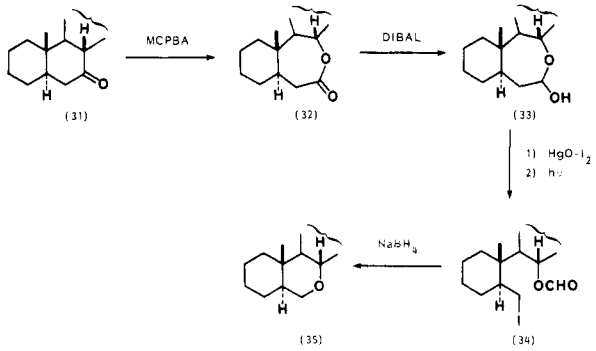


a 1:1 crystalline mixture of 3-oxa-*A*-homo-5α-cholestan-4-one (**18**) and 4-oxa-*A*-homo-5α-cholestan-3-one (**19**). Reduction of this mixture with DIBAL in dry toluene at −78 °C afforded a crystalline mixture of 3-oxa-*A*-homo-5α-cholestan-4-ols **20** and 4-oxa-*A*-homo-5α-cholestan-3-ols **21**. The mixture of the lactols in benzene was subjected to the hypoiodite photolysis under the conditions as described for lactol **13** to give a mixture of formates **22** and **23** in a 66% yield. The mixture of formates in the presence of $NaBH_4$ in THF was heated under reflux to give 3-oxa-5α-cholestane in a 74% yield. This example demonstrates that the transformation of cyclic ketones into cyclic ethers can readily be achieved even when Baeyer–Villiger oxidation of the ketones leads to the mixture of the two isomeric lactones.

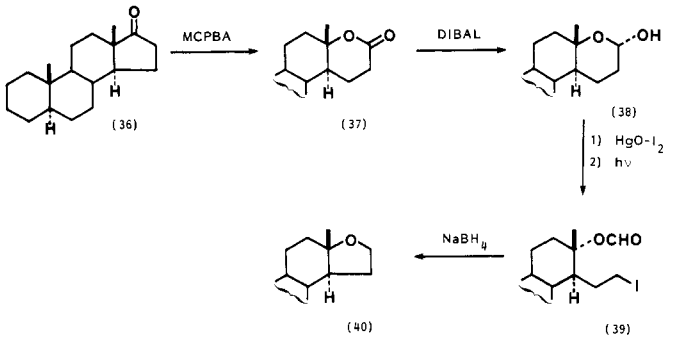
4-Oxa-5α-cholestane (30) (Scheme IV). Baeyer–Villiger oxidation of 5α-cholestan-4-one (**25**) with MCPBA proceeds regioselectively and gives 4a-oxa-*A*-homo-5α-cholestan-4-one (**26**)[10] as a single product in a 63% yield. The reduction of lactone **26** with DIBAL as described above gave the corresponding crystalline lactol **27**. The lactol **27** in solution, however, was found to be in an equilibrium with its ring-opened aldehyde **28**. Its ^1H NMR

(7) Ahmad, N. S.; Moinuddin, G.; Khan, I. A. *J. Org. Chem.* **1978**, *43*, 163.
(8) Schmidtlin, J.; Wettstein, A. *Angew. Chem., Int. Ed. Engl.* **1964**, *3*, 240.
(9) Jacobs, T. L.; Brownfield, R. B. *J. Am. Chem. Soc.* **1960**, *82*, 4033.
(10) Klyne, W.; Kirk, D. N.; Tilley, J.; Suginome, H. *Tetrahedron* **1980**, *36*, 1543.

Scheme V



Scheme VI

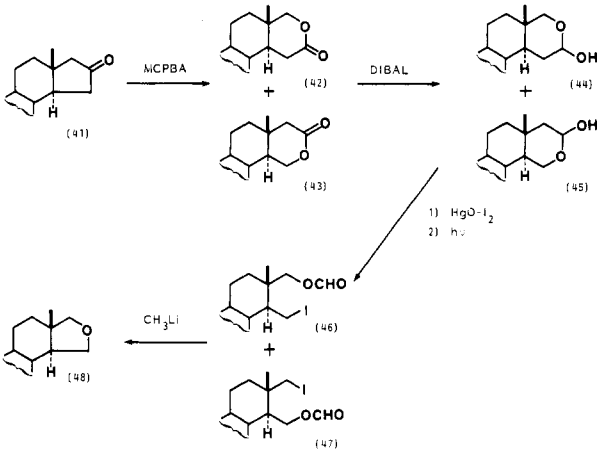


indicated that the ratio of lactol **27** to aldehyde **28** in $CDCl_3$ was 2:1. The transformation of the lactol into formate **29** resulted in a reduced yield (51%) of formate **29**; this is apparently due to a similar equilibrium in benzene. The cyclization of form ate **29** to 4-oxa-5α-cholestane (**30**) with $NaBH_4$ could not be achieved but an oxasteroid (**30**) was obtained in an 84% yield by the treatment of **29** with methyllithium in THF. Because of their biological activity, 4-oxasteroids have been the target for synthesis by four groups of investigators.[11-14] The present methodology perhaps provides the simplest route to these valuable steroids.

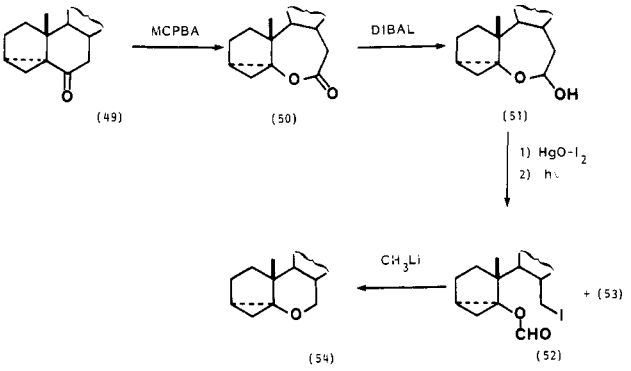
7-Oxa-5α-cholestane (35) (Scheme V). Baeyer–Villiger oxidation of 5α-cholestan-7-one (**31**)[15] with MCPBA gave a crystalline 7a-oxa-*B*-homo-5α-cholestan-7-one (**32**) in an 89% yield. The reaction was regioselective and no isomeric lactone was formed. The reduction of lactone **32** with DIBAL to lactol **33** followed by the photolysis of its hypoiodite afforded a formate (**34**) in a 94% yield. The treatment of **34** with $NaBH_4$ in a boiling THF resulted in the formation of a hitherto undescribed 7-oxa-5α-cholestane (**35**) in a 74% yield.

17-Oxa-5α-androstane (40)[6] (Scheme VI). This transformation is a typical example in which the stereochemical integrity of the chiral center adjacent to the carbonyl group of the starting cyclic ketone is maintained. Baeyer–Villiger oxidation of 5α-androstan-17-one (**36**) in dichloromethane with MCPBA gave a crystalline 17a-oxa-*D*-homo-5α-androstan-17-one (**37**) in an 85% yield. The oxidation was again regioselective. The reduction of

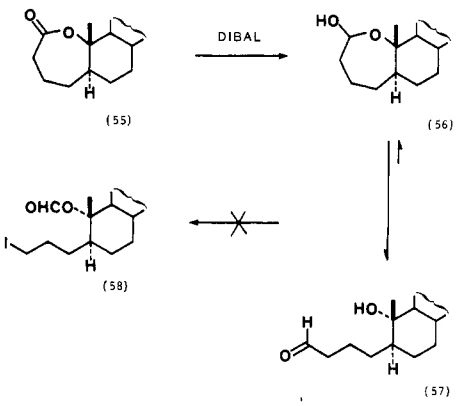
Scheme VII



Scheme VIII



Scheme IX



lactone **37** with DIBAL gave the corresponding lactol **38** smoothly; this was converted into a crystalline formate (**39**) by the photolysis of its hypoiodite. The formate **39** gave 17-oxa-5α-androstane (**40**)[6] by the treatment with $NaBH_4$ in a boiling THF.

16-Oxa-5α-androstane (48) (Scheme VII). Baeyer–Villiger oxidation of 5α-androstan-16-one (**41**)[15] with MCPBA gave a 9:1 crystalline mixture of 17-oxa-*D*-homo-5α-androstan-16-one (**42**) and 16-oxa-*D*-homo-5α-androstan-17-one (**43**) in an 80% yield. The mixture was reduced with DIBAL to give a mixture of lactols **44** and **45**. The transformation of this mixture into a mixture of formates **46** and **47** was achieved in a 60% yield. The mixture could be cyclized to a new oxasteroid, 16-oxa-5α-androstane (**48**), with methyllithium in 74% yield.

6-Oxa-3α,5-cyclo-5α-cholestane (54) (Scheme VIII). A carbonyl group of a steroidal cyclopropyl ketone can be replaced by an oxygen atom by the present method. Thus,

(11) Fieser, L. F.; Goto, T.; Bhattachryya, B. K. *J. Am. Chem. Soc.* **1960**, *82*, 1700.
(12) Edward, J. T.; Morand, P. F. *Can. J. Chem.* **1960**, *38*, 1325.
(13) Doorenbos, N. J.; Wu, M. T. *J. Org. Chem.* **1961**, *26*, 4550.
(14) Pettit, G. R.; Kasturi, T. R. *J. Org. Chem.* **1961**, *26*, 4557.
(15) Bridgeman, J. E.; Jones, E. R. H.; Meakins, G. D.; Wicha, J. *J. Chem. Soc., Chem. Commun.* **1967**, 898. Bridgeman, J. E.; Butchers, C. E.; Jones, E. R. H.; Kasal, A.; Meakins, G. D.; Woodgate, P. D. *J. Chem. Soc. C* **1970**, 244.

Baeyer–Villiger oxidation of 3α,5-cyclo-5α-cholestan-6-one (**49**) gave 6-oxa-*B*-homo-3α,5-cyclo-5α-cholestan-7-one (**50**) as a single lactone in an 83% yield. The reduction of the lactone with DIBAL afforded 6-oxa-*B*-homo-3α,5-cyclo-5α-cholestan-7-ol (**51**) in a 90% yield. The photolysis of its hypoiodite gave an iodo formate (**52**) in a 14% yield plus an iodine-containing unstable byproduct (**53**). The ^{1}H NMR spectrum of the byproduct **53** indicated that it had no cyclopropane ring. The cyclization of iodo formate **52** with methyllithium afforded a novel oxasteroid (**54**) in an 85% yield.

The Attempted Conversion of 5α-Cholestan-1-one into 1-Oxa-5α-cholestan-1-one (Scheme IX). The carbonyl group of 5α-cholestan-1-one could not be replaced by an oxygen atom by the present method. Baeyer–Villiger oxidation of 5α-cholestan-1-one gave 1-oxa-*A*-homo-5α-cholestan-2-one (**55**) which was reduced with DIBAL to 1-oxa-*A*-homo-5α-cholestan-2β-ol (**56**). The lactol was, however, totally in the form of a ring-opened aldehyde (**57**) in solution and no lactol was detected by ^{1}H NMR spectroscopy. This finding is in agreement with our previous observation that a very low yield of formate **58** could only be obtained in the photolysis of the hypoiodite of 5α-cholestan-1α-ol.[6]

Conclusions. The foregoing results may demonstrate that the replacement of the carbonyl group of cyclic ketones can be achieved under very mild conditions in excellent overall yield without applying strong oxidizing reagents.

Studies of the further extention of the scope of the present method are in progress and will be reported in due course.

Experimental Section

General Methods. For the instruments used and the general procedure of the photolysis, see reference 6.

General Procedure. Transformation of 5α-Cholestan-6-one (11) into 6-Oxa-5α-cholestane (16). 6-Oxa-*B*-homo-5α-cholestan-7-one (12).[7] This lactone was prepared by the reported procedure: mp 157–159 °C (lit.[7] mp 155 °C).

6-Oxa-*B*-homo-5α-cholestan-7ξ-ol (13). To a solution of lactone **12** (380 mg) in dry toluene (42 mL) at −78 °C cooled by dry ice–methanol was added dropwise diisobutylaluminum hydride (DIBAL) 20% in hexane (Ventron) (1.3 mL) within the course of 10 min. The solution was stirred for 2 h at −78 °C and poured into ice water. After the removal of the precipitates, the solution was washed with water and dried over anhydrous Na_2SO_4. The usual workup gave a crude lactol (**13**) (405 mg) which was recrystallized from methanol–acetone to yield the 7ξ-ol (365 mg): mp 136.5–137.5 °C; IR 3300 (OH), 1139, 1011 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 0.86 (3 H, s, 19-H), 2.65 (1 H, br s, OH), 3.80 (1 H, dd, J = 10.25, 5.85 Hz, 5α-H), 5.09 (1 H, br s, 7α-H); MS, m/e 404 (M^+, 6%), 386 ($M^+ - H_2O$, 48) 249 (75), 136 (68), 95 (85), 81 (90), 55 (100), 43 (71). Anal. Calcd for $C_{27}H_{48}O_2$: C, 80.14; H, 11.96. Found: C, 79.70; H, 12.13.

Irradiation of Hypoiodite of 6-Oxa-*B*-homo-5α-cholestan-7ξ-ol (13) in the Presence of Mercury(II) Oxide and Iodine. To the lactol **13** (200 mg) in dry benzene (25 mL) containing pyridine (0.7 mL) was added mercury(II) oxide (214 mg) and iodine (251 mg). The solution in a Pyrex vessel was flushed with nitrogen and irradiated by a 100-W high-pressure Hg arc. The irradiation was discontinued after 2 h. The solution was filtered and the filtrate was worked up in the usual manner to give a crude oily product (281 mg). This product was subjected to preparative TLC with benzene to yield three fractions A, B, and C in the order of decreasing mobility.

Fraction A (237 mg, 90%) was the formate **15**: IR 1720 (CHO), 1180 cm^{-1} (OCHO); ^{1}H NMR ($CDCl_3$) δ 0.70 (3 H, s, 18-H), 0.88 (3 H, s, 19-H), 3.41 (1 H, dd, J = 10.75, 2.45 Hz, 7-H), 3.62 (1 H, dd, J = 10.75, 1.60 Hz, 7-H), 5.19 (1 H, br s, 5α-H), 8.09 (1 H, s, OCHO); MS, m/e (relative intensity) 530 (M^+, 0.3), 484 ($M^+ - OCH_2O$, 3), 403 ($M^+ - I$, 2), 357 ($M^+ - OCH_2O - I$, 50), 95 (100); high-resolution mass calcd for $C_{27}H_{47}IO_2$ 530.2620, found 530.2630.

Fractions B (4 mg) and C (12 mg) were the lactone **12** and the starting lactol.

Preparation of 6-Oxa-5α-cholestane (16). The formate **15** (70 mg) and $NaBH_4$ (70 mg) in THF (10 mL) were heated under reflux for 10 h. After the removal of the solvent under reduced pressure, the residue was dissolved in diethyl ether. The solution was washed with water and brine and dried over anhydrous Na_2SO_4. Evaporation of the solvent gave a crude 6-oxa-5α-cholestane which was then subjected to preparative TLC with benzene to give 6-oxa-5α-cholestane. It was recrystallized from acetone–methanol to yield crystals (37 mg, 75%): mp 62.0–62.5 °C; IR 1123, 1101, 981 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 0.88 (3 H, s, 19-H), 2.91 (1 H, dd, J = 10.74, 4.40 Hz, 7-H), 3.86 (1 H, dd, J = 10.74, 4.90, 7-H), 3.09 (1 H, dd, J = 11.23, 10.75, 5α-H); MS, m/e (relative intensity) 374 (M^+, 37), 219 (100), 201 (33), 164 (28). Anal. Calcd for $C_{26}H_{46}O$: C, 83.35; H, 12.38. Found: C, 83.20: H, 12.23.

Preparation of 3-Oxa-5α-cholestane (24). Baeyer–Villiger oxidation of 5α-cholestan-3-one (**17**) (1.5 g) with MCPBA (3 g) and *p*-toluenesulfonic acid (0.5 g) in dichloromethane for 5 h gave a crude product. Recrystallization from methanol–acetone gave a mixture of 3-oxa-*A*-homo-5α-cholestan-4-one (**18**) and 4-oxa-*A*-homo-5α-cholestan-3-one (**19**) (1.04 g): mp 182–184 °C. Reduction of the lactones (600 mg) in dry toluene with DIBAL in hexane (2.2 mL) for 1 h at −78 °C gave a crude product (612 mg) which was recrystallized from methanol–acetone to yield a mixture of 3-oxa 4-ol **20** and 4-oxa 3-ol **21** (547 mg): mp 114–117 °C; IR 3370, 1100, 1071, 1044 cm^{-1}; high-resolution mass calcd for $C_{27}H_{48}O_2$ 404.3654, found 404.3671. To the mixture of lactols (300 mg) in dry benzene (37 mL) containing pyridine (1 mL) was added mercury(II) oxide (242 mg) and iodine (283 mg). The solution was irradiated for 2 h and worked up by the usual method to give a crude oily product (381 mg). This was subjected to preparative TLC with benzene to yield three fractions. The most TLC mobile fraction (218 mg) was oily formates **22** and **23**: IR (neat) 1727 (OCHO), 1172 cm^{-1}; high-resolution mass calcd for $C_{27}H_{47}IO_2$ 530.2621, found 530.2624.

The second and third mobile fractions (50 mg and 48 mg) were a mixture of the two lactones and the starting lactol. A solution of the formates **22** and **23** (200 mg) and $NaBH_4$ (200 mg) in THF (15 mL) was heated under reflux for 3 h to give crude 3-oxa-5α-cholestane (**24**) (154 mg) which was recrystallized from methanol to yield an analytically pure specimen (104 mg).

Preparation of 4-Oxa-5α-cholestane (30). 4a-Oxa-*A*-homo-5α-cholestan-4-ol (**27**). Reduction of 4a-oxa-*A*-homo-5α-cholestan-4-one (**26**) (200 mg) in dry toluene (20 mL) with 20% DIBAL in hexane (0.73 mL) for 2 h gave crude lactol which was recrystallized from acetone to yield the 4-ol **27**: mp 111–114 °C (170 mg); IR 3400, 3280, 1236, 1151, 1121, 1062, 1048, 1026, 985 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 0.64 (3 H, s, 18-H of a lactol and an aldehyde), 0.88 (3 H, s, 19-H of a lactol and an aldehydee, 2.40–2.45 (0.66 H, m, 3-methylene of the aldehyde form), 3.66 (0.33 H, m, 5α-H of the aldehyde form), 3.70 (0.66 H, dd, J = 10.74, 5.37 Hz, 5α-H of the lactol form), 5.14 (0.66 H, m, 4-H of the lactol form), 9.79 (0.33 H, t, J = 1.2 Hz, CHO of the aldehyde form); MS, m/e (relative intensity) 404 (M^+, 0.7), 386 ($M^+ - H_2O$, 4), 332 (100), 95 (23), 81 (34), 69 (29), 57 (32), 55 (38), 43 (38). Anal. Calcd for $C_{27}H_{48}O_2$: C, 80.14; H, 11.96. Found: C, 79.89; H, 11.95. To the lactol **27** (150 mg) in dry benzene (219 mL) containing pyridine (0.5 mL) was added mercury(II) oxide (161 mg) and iodine (189 mg). The solution was irradiated for 70 min and worked up in the usual manner to give a crude oily product. The product was subjected to preparative TLC with benzene to yield fractions A and B in order of decreasing mobility.

Fraction A (100 mg) was an oily formate (**29**): IR 1722 (CHO), 1178 cm^{-1} (OCHO); ^{1}H NMR ($CDCl_3$) δ 0.94 (3 H, s, 19-H), 3.13 (2 H, m, 3-H), 4.79 (1 H, dd, J = 10.1, 5.3 Hz, 5α-H); MS, m/e (relative intensity) 530 (M^+, 0.8), 484 ($M^+ - OCH_2O$, 35), 403 ($M^+ - I$, 1), 357 (17), 330 (20), 287 (67), 84 (75), 78 (100), 69 (61), 57 (68), 55 (62), 43 (70); high-resolution mass calcd for $C_{27}H_{47}IO_2$ 530.2621, found 530.2644.

A solution of the formate **29** (27 mg) in THF (10 mL) was cooled at −78 °C by dry ice–methanol. To this solution was added dropwise methyllithium in diethyl ether (1 M, solution) (0.11 mL) while stirring. After the solution had been stirred for 3 h at −78 °C, the temperature of the solution rose to room temperature.

Evaporation of the solvent left a residue which was dissolved in diethyl ether. The solution was worked up in the usual way to yield a crystalline 4-oxa-5α-cholestane (**30**) (22 mg). This was purified by preparative TLC (benzene) to yield crystals (16 mg). The specimen for analysis was obtained by recrystallization from methanol: mp 89.5–90.5 °C (lit.[11] mp 94–95 °C; lit.[12] mp 89–90 °C; lit.[13] mp 93–94 °C; lit.[14] mp 91–92 °C); ^{1}H NMR ($CDCl_3$) δ 0.92 (3 H, s, 19-H), 2.92 (1 H, dd, J = 11.4, 4.4 Hz, 5α-H), 3.36–3.49 (1 H, m, 3-H), 3.93–4.01 (1 H, m, 3-H); MS, m/e 374 (M^+, 54), 359 (M^+ – Me, 7), 219 (100), 149 (29), 85 (24), 57 (25), 55 (30), 43 (71).

Preparation of 7-Oxa-5α-cholestane (35). Baeyer–Villiger oxidation of 5α-cholestan-7-one (**31**) (600 mg) in dichloromethane (30 mL) with MCPBA (900 mg) and p-toluenesulfonic acid (290 mg) for 5 h gave a crude product which was subjected to preparative TLC with a 10:1 benzene–diethyl ether to yield 7a-oxa-*B*-homo-5α-cholestan-7-one (**32**) (558 mg). Analytically pure specimens were obtained by recrystallizing it from acetone–methanol: mp 120–121 °C and then 128–130 °C; IR 1727, 1033, 1020 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 0.97 (3 H, s, 19-H), 2.03 (1 H, d, J = 14.2 Hz, 6-H), 2.77 (1 H, dd, J = 14.2, 10.7 Hz, 6-H), 4.19 (1 H, dd, J = 10.5, 8.4 Hz, 8-H); MS, m/e (relative intensity) 402 (M^+, 17), 387 (M^+ – Me, 13), 135 (63), 109 (49), 95 (100). Anal. Calcd for $C_{27}H_{46}O_2$: C, 80.54; H, 11.51. Found: C, 80.43; H, 11.46.

Reduction of the lactone **32** (400 mg) in dry toluene (40 mL) with DIBAL in hexane (1.5 mL) for 2 h at −78 °C gave a crude product which was recrystallized from methanol–acetone to yield 7a-oxa-*B*-homo-5α-cholestan-7-ol (**33**) (377 mg): mp 159.5–161.5 °C; IR 3370, 1113, 1016 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 0.84 (3 H, s, 19-H), 2.16 (1 H, d, J = 2.44 Hz, OH), 3.76 (1 H, t, J = 9.5 Hz, 8-H), 5.11 (1 H, ddd, J = 8.30, 5.86, 2.44, 7-H); MS, m/e (relative intensity) 404 (M^+, 0.9), 386 (M^+ – H_2O, 3), 343 (37), 203 (21), 135 (66), 95 (100). Anal. Calcd for $C_{27}H_{48}O_2$: C, 80.14; H, 11.96. Found: C, 80.07; H, 11.95.

To lactol **33** (200 mg) in dry benzene (25 mL) containing pyridine (0.5 mL) was added mercury(II) oxide (214 mg) and iodine (250 mg). The solution was irradiated for 1 h 40 min while stirring and worked up by the usual method to give an oily product (298 mg). This was subjected to preparative TLC with benzene to yield two fractions. The more mobile fraction was the oily formate **34** (247 mg): IR 1720, 1180 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 0.74 (3 H, s, 18-H), 0.90 (3 H, s, 19-H), 2.74 (1 H, dd, J = 10.75, 9.76 Hz, 6-H), 3.36 (1 H, dd, J = 9.76, 1.0 Hz, 16-H), 5.25 (1 H, dd, J = 10.25, 9.77 Hz, 8β-H), 8.04 (1 H, s, OCHO); MS, m/e (relative intensity) 484 (M^+ – OCH_2O, 0.1), 403 (M^+ – I, 1), 357 (17), 135 (67), 109 (100); high-resolution mass calcd for $C_{27}H_{47}O_2$ (M^+ – I) 403.3576, found 403.3588. The less mobile fraction (11 mg) was the lactone **32**. A solution of the formate **34** (215 mg) and $NaBH_4$ (200 mg) in THF (25 mL) was heated under reflux for 21 h to give a crude 7-oxa-5α-cholestane (**35**) which was recrystallized from methanol–acetone to yield a pure specimen (112 mg): mp 89.5–91.0 °C; IR 1096, 975 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 0.91 (3 H, s, 19-H), 3.28–3.47 (3 H, m, 6α-, 6β-, 8β-H); MS, m/e (relative intensity) 374 (M^+, 7), 359 (M^+ – Me, 7), 219 (100), 165 (38), 109 (25). Anal. Calcd for $C_{26}H_{46}O$: C, 83.35; H, 12.38. Found: C, 83.33; H, 12.42.

17-Oxa-5α-androstane (40). Baeyer–Villiger oxidation of 5α-androstan-17-one (**36**) (860 mg) in dichloromethane (75 mL) with MCPBA (1.6 g) and p-toluenesulfonic acid (860 mg) for 5 h gave a crude product which was recrystallized from methanol–water to yield 17a-oxa-*D*-homo-5α-androstan-17-one (**37**) (770 mg): mp 138–139 °C; IR 1728, 1116, 1070 cm^{-1}; ^{1}H NMR δ 0.75 (3 H, s, 19-H), 1.29 (3 H, s, 18-H); MS, m/e (relative intensity) 290 (M^+, 2), 275 (M^+ – Me, 32), 218 (100). Anal. Calcd for $C_{19}H_{30}O_2$: C, 78.57; H, 10.41. Found: C, 78.49; H, 10.23. Reduction of lactone **37** (630 mg) in dry toluene (70 mL) with 20% DIBAL in hexane (3 mL) for 1 h at −78 °C gave a crude lactol (632 mg) which was recrystallized from acetone–dichloromethane to yield 17α-ol **38**: mp 158–160 °C (550 mg) as a sole lactol; IR 3360, 1126, 969, 957 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 0.74 (3 H, s, 19-H), 1.16 (3 H, s, 18-H), 2.98 (1 H, d, J = 6.83 Hz, OH), 5.05 (1 H, ddd, J = 9.77, 6.83, 2.93 Hz, 17β-H); MS, m/e (relative intensity) 292 (M^+, 0.7), 274 (M^+ – H_2O, 25), 218 (100), 109 (43). Anal. Calcd for $C_{19}H_{32}O_2$: C, 78.03; H, 11.03. Found: C, 77.87; H, 11.08. To the lactol **38** (80 mg) in dry benzene (20 mL) containing pyridine (0.5 mL) were added mercury(II) oxide (89 mg) and iodine (104 mg). The solution in a Pyrex vessel was flushed with nitrogen and irradiated for 1 h and worked up in the usual manner to give a crude crystalline product (106 mg). The product was subjected to preparative TLC with benzene to yield fractions A, B, and C in the order of decreasing mobility; fraction A (74 mg) was a crystalline formate (**39**). Specimens for the analysis, mp 70–72 °C, were obtained by recrystallizing the crude product from methanol–acetone: IR 1721, 1203, 1170, 1123 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 0.72 (3 H, s, 19-H), 1.43 (3 H, s, 18-H), 3.13–3.28 (2 H, m, 16-H), 8.04 (1 H, s, OCHO); MS, m/e (relative intensity) 372 (M^+ – OCH_2O, 18), 291 (M^+ – I, 12), 245 (M^+ – OCH_2O – I, 100), 217 (35), 149 (57), 135 (63), 109 (99), 95 (66), 81 (66), 67 (54), 55 (54); high-resolution mass calcd for $C_{18}H_{29}I$ (M^+ – OCH_2O) 372.1311, found 372.1310, found 372.1310. Fractions B and C were lactone **37** (16 mg) and the starting 17α-ol **38**. The formate **39** (50 mg) and $NaBH_4$ (50 mg) in THF (6 mL) was heated under reflux for 3 h to give 17-oxa-5α-androstane (**40**) which was purified by means of preparative TLC (benzene) and recrystallized from methanol to yield a pure specimen (23 mg).

Preparation of 16-Oxa-5α-cholestane (48). Baeyer–Villiger oxidation of 5α-androstan-16-one (**41**) (400 mg), prepared according to the method by Meakins et al.,[15] in dichlorométhane (35 mL) with MCPBA (800 mg) and p-toluenesulfonic acid (400 mg) overnight gave a crude product which was recrystallized from methanol–acetone to yield a 9:1 mixture of 17-oxa-*D*-homo-5α-androstan-16-one (**42**) and 16-oxa-*D*-homo-5α-androstan-17-one (**43**) (336 mg). After several recrystallizations the crystals melted at 193–195 °C; IR 1722 cm^{-1}; MS, m/e (relative intensity) 290 (M^+ 100). Anal. Calcd for $C_{19}H_{30}O_2$: C, 78.57; H, 10.41. Found: C, 78.46; H, 10.31. Reduction of the lactones **42** and **43** (360 mg) in dry toluene (40 mL) with DIBAL in hexane (1.8 mL) for 3 h gave a crude product (362 mg) which was recrystallized from methanol to yield a mixture of 17-oxa 16-ol **44** contaminated with 16-oxa 17-ol **45** (345 mg): IR 3340 cm^{-1}; MS, m/e (relative intensity) 292 (M^+, 13). Anal. Calcd for $C_{19}H_{32}O_2$: C, 78.03; H, 11.03. Found: C, 77.91; H, 11.01.

To the lactols **44** and **45** (200 mg) in dry benzene (34 mL) containing pyridine (0.5 mL) were added mercury(II) oxide (297 mg) and iodine (348 mg). The solution was irradiated for 1 h 40 min and was worked up by the usual method to give a crude crystalline product (267 mg). This product was subjected to preparative TLC with benzene to yield two fractions. The more TLC mobile fraction (173 mg) was a mixture of formates **46** and **47**. A specimen for analysis was obtained by recrystallization from acetone–methanol: mp 48–52 °C; IR 1724, 1182 cm^{-1}; high-resolution mass calcd for $C_{19}H_{31}IO_2$ 418.1369, found 418.1386. Another fraction (75 mg) was the lactone.

A solution of the formate **46** and **47** (65 mg) in THF (20 mL) was treated with methyllithium in diethyl ether as in the case of the preparation of 4-oxa-5α-cholestane (**30**) to give crude crystalline 16-oxa-5α-androstane (**48**) (46 mg). This was purified once by preparative TLC (benzene) and then recrystallized from methanol–water: mp 78–80 °C; IR 1019, 894 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 0.81 (3 H, s, 19-H), 0.92 (3 H, s, 18-H), 3.29 (1 H, d, J = 7.32 Hz, 17-H), 3.59 (1 H, d, J = 7.32 Hz, 17-H), 3.42 (1 H, dd, J = 11.23, 7.32 Hz, 15β-H), 3.87 (1 H, dd, J = 7.32, 6.83 Hz, 15α-H); MS, m/e (relative intensity) 262 (M^+ 10), 247 (M^+ – Me, 5), 231 (100), 217 (15), 149 (27), 109 (49), 95 (43), 81 (48), 67 (45), 55 (43), 41 (43). Anal. Calcd for $C_{18}H_{30}O$: C, 82.38; H, 11.52. Found: C, 82.05; H, 11.54.

Preparation of 3α,5-Cyclo-6-oxa-5α-cholestane (54). Baeyer–Villiger oxidation of 3α,5-cyclo-5α-cholestan-6-one (**49**) (450 mg) in dichloromethane (15 mL) with MCPBA (675 mg) and p-toluenesulfonic acid (200 mg) overnight gave a crude product which was recrystallized from methanol–acetone to yield 3α,5-cyclo-6-oxa-*B*-homo-5α-cholestan-7-one (**50**) (390 mg): mp 126–128 °C; IR 1735, 1260, 1217, 1123, 1089, 1048 cm^{-1}; ^{1}H NMR δ 0.71 (3 H, s, 18-H), 1.05, (3 H, s, 19-H), 2.42 (1 H, dd, J = 13.8, 8.3 Hz, 7a-H), 2.59 (1 H, dd, J = 13.8, 2.44, 7a-H); MS, m/e (relative intensity) 400 (M^+, 63), 385 (54), 372 (55), 318 (54), 247 (76), 111 (98), 95 (100). Anal. Calcd for $C_{27}H_{44}O_2$: C, 80.94; H, 11.07. Found: C, 80.58; H, 10.96.

Reduction of the lactone **50** (300 mg) in dry toluene (20 mL) with 1 M DIBAL in hexane (1.0 mL) for 2 h gave an oily product (299 mg). The product was purified by preparative TLC to yield an oily lactol (**51**) (272 mg): IR (neat) 3360, 1033, 1005 cm^{-1}; ^{1}H

NMR ($CDCl_3$) δ 0.70 (3 H, s, 18-H), 1.04 (3 H, s, 19-H), 5.03 (1 H, m, 7-H); MS, *m/e* (relative intensity) 402 (M^+, 0.7), 111 (100), 84 (73); high-resolution mass calcd for $C_{27}H_{46}O_2$ 402.3498, found 402.3545.

To the lactol **51** (60 mg) in dry benzene (8 mL) containing pyridine (0.1 mL) was added mercury(II) oxide (65 mg) and iodine (76 mg). The solution was irradiated for 1.5 h to give a crude oily product (85 mg). This was subjected to preparative TLC with benzene to yield three fractions. The most TLC mobile fraction (11 mg) was an oily formate (**52**): IR (neat) 1738 (OCHO), 1160 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.75 (3 H, s, 18-H), 1.46 (3 H, s, 19-H), 3.34 and 3.57 (each 1 H, d, J = 9.76 Hz, 7-H), 8.16 (1 H, s, OCHO); MS, *m/e* (relative intensity) 528 (M^+, 2), 482 ($M^+ - OCH_2O$, 3), 459 (16), 401 ($M^+ - I$, 2), 111 (100) 95 (79); high-resolution mass calcd for $C_{27}H_{45}IO_2$ 528.2463, found 528.2478. The second (15 mg) and the third fractions were lactone **50** and a mixture of unidentified products. A solution of the formate **52** (30 mg) in THF (10 mL) was treated with methyllithium in diethyl ether (1 M, solution) (0.12 mL) as in the case of 4-oxa-5α-cholestane (**30**) to yield a crystalline 3α,5-cyclo-6-oxa-5α-cholestane (**54**) (25 mg). This was recrystallized from methanol to yield pure needles (18 mg): mp 95.5–97.5 °C; IR 1250, 1091, 1007 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.55–0.69 (1 H, m, 3-H), 0.72 (3 H, s, 18-H), 1.03 (3 H, s, 19-H), 3.09 (1 H, t, J = 10.75 and 10.75 Hz, 7α-H), 3.6. (1 H, dd, J = 10.75 and 4.2 Hz, 7β-H); MS, *m/e* (relative intensity) 372 (M^+, 100), 111 (89); high-resolution mass calcd for $C_{26}H_{44}O$ 372.3392, found 372.3412.

Reduction of 1-Oxa-*A*-homo-5α-cholestan-2-one (55). To a solution of the lactone **55** (340 mg) in dry toluene (40 mL) cooled at −78 °C was added dropwise DIBAL in hexane (1.25 mL). The solution was stirred for 1.5 h at −78 °C and poured into iced water. After the solution had been filtered, the filtrate was worked by the usual method to yield lactol **56**; this was in the form of a ring-opened aldehyde (340 mg) (**57**): IR (neat) 3410 (OH) and 1722 cm^{-1} (CHO); ^1H NMR δ 0.66 (3 H, s, 18-H), 0.98 (3 H, s, 19-H), 2.33–2.55 (2 H, m, 2-H), 9.75 (1 H, t, J = 2, CHO); MS, *m/e* (relative intensity) 404 (M^+, 0.2), 386 ($M^+ - H_2O$, 0.2), 55 (26), 43 (100); high-resolution mass calcd for $C_{27}H_{48}O_2$ 404.3652, found 404.3647.

Registry No. **11**, 570-46-7; **12**, 31239-55-1; **13**, 93789-70-9; **15**, 93789-71-0; **16**, 93920-67-3; **17**, 566-88-1; **18**, 71766-31-9; **19**, 1982-71-4; **20**, 93789-73-2; **21**, 93789-74-3; **22**, 93789-81-2; **23**, 96616-58-9; **24**, 91796-74-6; **25**, 566-51-8; **26**, 58323-66-3; **27**, 93789-75-4; **28**, 96616-59-0; **29**, 93789-83-4; **30**, 2672-41-5; **31**, 567-71-5; **32**, 96616-60-3; **33**, 96616-61-4; **34**, 96616-62-5; **35**, 96647-92-6; **36**, 963-74-6; **37**, 2466-25-3; **38**, 96616-63-6; **39**, 83625-92-7; **40**, 83679-49-6; **41**, 1032-16-2; **42**, 60243-87-0; **43**, 93789-72-1; **44**, 93789-77-6; **45**, 93789-78-7; **46**, 93789-88-9; **47**, 93789-84-5; **48**, 93861-55-3; **49**, 3839-09-6; **50**, 31239-51-7; **51**, 96616-64-7; **52**, 96632-86-9; **54**, 96616-65-8; **55**, 96616-66-9; **57**, 96616-67-0.

Agelasidines. Novel Hypotaurocyamine Derivatives from the Okinawan Sea Sponge *Agelas nakamurai* Hoshino†

Hideshi Nakamura,*‡ Houming Wu,[1,‡] Jun'ichi Kobayashi,‡ Masaki Kobayashi,‡ Yasushi Ohizumi,‡ and Yoshimasa Hirata§

Mitsubishi-Kasei Institute of Life Sciences, 11 Minamiooya, Machida-shi, Tokyo 194, Japan, and Faculty of Pharmacy, Meijo University, Nagoya 468, Japan

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Two new diterpene derivatives of hypotaurocyamine, agelasidine B (**2a**) and agelasidine C (**3a**), have been isolated from the Okinawan sea sponge *Agelas nakamurai* Hoshino. The structures of agelasidine B and agelasidine C were elucidated by interpretation of spectral data and chemical degradation experiments. The agelasidines show inhibitory effects on growth of microorganisms, contractile responses of smooth muscle, and enzymic reactions of Na,K-ATPase.

Recent studies on bioactive metabolites of sea sponges of the genus *Agelas* revealed the presence of sesqui- and diterpenes with polar functionalities possessing inhibitory effects on growth of microorganisms,[4] contractile responses of smooth muscles,[6] and enzymic reactions of Na,K-ATPase.[3,5] A quarternary 9-methyladenine derivative of an unidentified bicyclic dideterpene has been reported as a constituent of the sea sponge *Agelas dispar* by Cullen and Devlin.[2] Recently, quaternary 9-methyladenine derivatives of bicyclic diterpenes, agelasine A (**4**), agelasine B (**5**), agelasine C (**6**), agelasine D (**7**), and ageline B (**8**), and monocyclic diterpenes, agelasine E (**9**) and ageline A (agelasine F, **10**),[7] have been isolated from the Okinawan sea sponge *A. nakamurai* by us[3,5] and from a Pacific sea sponge *A.* sp. by Capon and Faulkner.[4] In contrast to the structural variety of the diterpene derivatives of 9-methyladenine, only one sesquiterpene derivative of hypotaurocyamine, agelasidine A (**1a**), has been reported as a constituent of the two sponges.[4,6] Our further study on physiologically active metabolites of the sponge resulted in the isolation of two novel diterpene derivatives of hypotaurocyamine, named agelasidine B and C. In this paper, we report the structural elucidation of agelasidine B (**2a**) and C (**3a**) (Figures 1 and 2).

Specimens of *A. nakamurai* were collected at Zampa Cape, Okinawa, using SCUBA (-10 to -20 m) and stored at -20 °C until needed. The chloroform-soluble material from the methanolic extracts of the sponge was chromatographed on a silica gel column with 3:12:2:2 chloroform-

† Physiologically active marine natural products from Porifera VIII.

‡ Mitsubishi-Kasei Institute of Life Sciences.

§ Faculty of Pharmacy, Meijo University.

(1) Permanent address: Shanhai Institute of Organic Chemistry, academia Sinica, 345 Linglin Lu, Shanghai, China.

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