for 7 hr led quantitatively to a mixture of the pseudo-acid chlorides **8a** and **8b** (1:2.5, respectively).

The tricyclic diamine **11**[19] was synthesized from acridine by a simple three-step procedure. Oxidation of acridine with ozone (2.2 equiv) in methanol at −40° followed by sodium borohydride (4.4 equiv) reduction of the ozonide resulted in the crystalline diol **10a** (43% yield), mp 115–118°. The diol was converted into the dimesylate **10b** in benzene–triethylamine with methanesulfonyl chloride (3 equiv) at 0° for 1 hr (85% yield). Exposure of **10b** to 15% concentrated ammonium hydroxide in methanol for 2 hr at room temperature gave the tricyclic diamine **11** after work-up (careful exclusion of oxygen) and purification by column chromatography (silica gel–methanol) (48% yield of **11** as tan crystals, mp 92.5–95°).[20]

The mixture of pseudo-acid chlorides **8a** and **8b** (1:2.5) was stirred with the tricyclic diamine **11** (0.85 equiv) in 10% pyridine–acetonitrile for 10 hr at room temperature, and the resulting amide mixture was cyclized using as medium 10% sodium acetate–acetic acid for 20 hr at 25°. After column chromatographic purification (a) on silica gel using 20% CH_3OH in $CHCl_3$ and (b) on silica gel using 3% CH_3OH in CH_2Cl_2, and finally preparative TLC on silica gel plates using 3% CH_3OH in CH_2Cl_2, the pure camptothecin 20-methoxycarbonyl derivative (**12a**) was obtained: uv (20% MeOH in $CHCl_3$) 258 nm (ϵ 20,600), 295 (5000), and 362 (18,100); $[\alpha]^{22}D$ +31.7° ($CHCl_3$).[21] The methoxy carbonyl group of **12a** was removed by reaction with lithium mercaptide in HMPA[22] yielding 90% of 20(*S*)-camptothecin (**12b**) identical in every respect with natural material:[23] found for synthetic **12b**, $[\alpha]^{22}D$ +31.1° (20% MeOH in $CHCl_3$), mp 275–278° dec; found for naturally derived camptothecin, $[\alpha]^{25}D$ +31.3° (20% MeOH in $CHCl_3$),[1] mp 276–278° dec.[24] The NMR, ir, uv, TLC, MS, and mixture melting point all confirmed the identity of synthetic and natural camptothecins.[25]

References and Notes

(1) (a) M. E. Wall, M. C. Wani, C. E. Cook, K. H. Palmer, A. T. McPhail, and G. A. Sim, *J. Am. Chem. Soc.*, **88**, 3888 (1966); (b) T. R. Govindachari and N. Viswanathan, *Phytochemistry*, **11**, 3529 (1972).

(2) A. T. McPhail and G. A. Sim, *J. Chem. Soc. B*, 923 (1968).

(3) (a) G. Stork and A. G. Schultz, *J. Am. Chem. Soc.*, **93**, 4074 (1971); (b) R. Volkman, S. Danishefsky, J. Eggler, and D. M. Solomon, *ibid.*, **94**, 3631 (1972); (c) M. Boch, T. Korth, J. M. Nelke, D. Pike, H. Radunz, and E. Winterfeld, *Chem. Ber.*, **105**, 2126 (1972); (d) C. Tang and H. Rapoport, *J. Am. Chem. Soc.*, **94**, 8615 (1972); (e) T. Sugasawa, T. Toyoda, and K. Sasakura, *Tetrahedron Lett.*, 5109 (1972); (f) A. I. Meyers, R. L. Nolen, E. W. Collington, T. A. Narwid, and R. C. Strickland, *J. Org. Chem.*, **38**, 1974 (1973); (g) A. S. Kende, T. J. Bentley, R. W. Draper, J. K. Jenkins, M. Joyeux, and J. Kubo, *Tetrahedron Lett.*, 1307 (1973); (h) M. Shamma, D. A. Smithers, and V. St. Georgiev, *Tetrahedron*, **29**, 1949 (1973); (i) M. C. Wani, H. F. Campbell, G. A. Brine, J. A. Kepler, M. E. Wall, and S. G. Levine, *J. Am. Chem. Soc.*, **94**, 3631 (1972).

(4) H. T. Abelson and S. Penman, *Nature* (*London*), *New Biol.*, **237**, 144 (1972).

(5) J. A. Edwards, A. Guzman, R. Johnson, P. J. Beeby, and J. H. Fried, *Tetrahedron Lett.*, 2031 (1974).

(6) The structures of all compounds reported in this communication were confirmed by ^1H NMR, ir uv, and mass spectral data on chromatographically homogeneous samples.

(7) R. Ratcliffe and R. Rodehorst, *J. Org. Chem.*, **35**, 4000 (1970).

(8) Ring metalation has been reported when this reaction is applied to various 3-furoic acid derivatives; see M. J. Jorgenson, *Org. React.*, **18**, 1 (1970).

(9) D. A. Evans, personal communication.

(10) T. A. Bither, W. H. Knoth, R. V. Lindsey, Jr., and W. H. Sharkey, *J. Am. Chem. Soc.*, **80**, 4151 (1958).

(11) (a) D. A. Evans and L. K. Truesdale, *Tetrahedron Lett.*, 4929 (1973). (b) The dicyclohexyl-18-crown-6-(LR3-301) was a gift from Dr. H. K. Frensdorff, E. I. du Pont de Nemours and Co., Wilmington, Del.

(12) The use of the stable *tert*-butyldimethylsilyl derivative was required to avoid desilylation in the next step which would lead to reversal of cyanohydrin formation; the trimethylsilyl cyanide analog of **4a** was not a satisfactory substrate.

(13) This procedure was found to be superior to the isolation of the resolved dihydroxy acid (**5a**) owing to the acid sensitivity and water solubility of **5a**.

(14) Both camptothecin $\{[\alpha]^{25}D$ +31.3° (MeOH)$\}$ and (+)-atrolactic acid $\{[\alpha]^{13.8}D$ +37.7° (EtOH)$\}$ have the *S* configuration[3,15] and a positive rotation; it was therefore anticipated that the (+)-lactone **6** should also be of the *S* configuration.

(15) J. H. Brewster, *J. Am. Chem. Soc.*, **78**, 4061 (1956).

(16) G. O. Schenck, *Justus Liebigs Ann. Chem.*, **584**, 156 (1953).

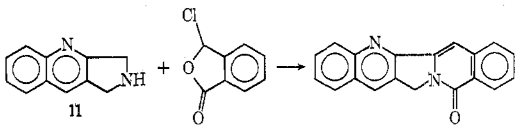
(17) Oxidation of the lactone **6** in methanol afforded a 1:1 mixture of pseudo-acids **7a** and **7b**.

(18) K. W. Ratts and W. G. Phillips, *J. Org. Chem.*, **39**, 3300 (1974).

(19) (a) M. C. Wani, J. A. Kepler, J. B. Thompson, M. E. Wall, and S. G. Levine, *Chem. Commun.*, 404 (1970); (b) L. H. Zalkow, J. B. Nabors, K. French, and S. C. Bisarya, *J. Chem. Soc. C*, 3551 (1971); (c) T. Tanaka, K. Mashimo, and M. Wagatsuma, *Tetrahedron Lett.*, 2803 (1971).

(20) See C. Dauth and H. G. O. Becker, *J. Prakt. Chem.*, **313**, 686 (1971).

(21) The yield of **12a** obtained in the coupling–cyclization process as described herein is ~6.5%. However, optimum conditions for this transformation have not been extensively studied owing to limitations of time and material (for example, a study of the variation of X in **7** may well be rewarding). It is noteworthy in this regard that the cyclization of the pseudo-acid chloride **i** with the tricyclic diamine (**11**) in a similar manner to that described for the production of **12a** yielded camptothecin analog **ii** in quantitative yield.



(22) P. A. Bartlett and W. S. Johnson, *Tetrahedron Lett.*, 4459 (1970).

(23) A sample of natural camptothecin was kindly supplied by Dr. M. E. Wall, Research Triangle Institute, Research Triangle Park, N.C.

(24) C. S. F. Tang, C. J. Morrow, and H. Rapoport, *J. Am. Chem. Soc.*, **97**, 159 (1975).

(25) This research was assisted financially by grants from the National Institutes of Health and the National Science Foundation. We are grateful to Dr. Harold C. Kluender for experimental contributions on the synthesis of the tricyclic intermediate **11**.

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Dry Ozonation. A Method for Stereoselective Hydroxylation of Saturated Compounds on Silica Gel

Summary: A convenient preparative method is described for hydroxylation of tertiary carbon atoms by ozonation of saturated compounds adsorbed on silica gel.

Sir: Ozone reacts slowly with saturated hydrocarbons inserting oxygen atoms into their C–H bonds, resulting in alcohols and ketones.[1] This insertion occurs preferentially at the tertiary carbon atoms, with a retention of configuration.

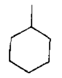
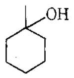
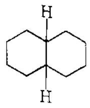
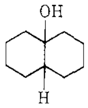
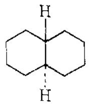
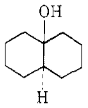
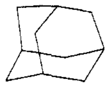
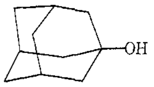
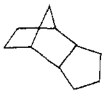
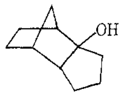
In spite of its preparative potentialities this reaction has been rarely used until now. One of the factors limiting the use of ozone as reagent for hydroxylation of saturated hydrocarbons is its low solubility in organic solvents. Even at low temperatures at which ozone forms stable solutions in saturated hydrocarbons and no reaction is observed, its solubility is slight (~0.1–0.3% by weight at −78°).[2] At higher temperatures necessary for reaction to proceed at reasonable rate, the solubility of O_3 is even smaller, necessitating prolonged ozonation periods.

Furthermore, the reactivity of ozone toward most of the organic solvents[3] limits its practical use as a hydroxylation reagent only to neat hydrocarbons.

Considering that silica gel adsorbs ozone efficiently at low temperatures[4] (its concentration being ~4.5% by weight at −78°), we have used the silica gel as the reaction matrix, thus overcoming the drawbacks arising from ozonations in solutions.

To perform the reaction we have pre-adsorbed the silica gel with the hydrocarbon[5] either by direct mixing or by im-

Table I
Reaction of Hydrocarbons with Ozone on Silica Gel

Substrate	Products	Yield,[a] %	Conversion,[a] %
		65[b]	>99.5
		79[c]	72
		76[d]	92
		99	>99.5
		72[e]	88
		99	>99.5
		90	>99.5

[a] Based on the quantity of the starting material consumed as determined by VPC analysis. [b] In addition to 34% of a mixture of the three methylcyclohexanones. [c] In addition to 0.6% of the epimeric alcohol. [d] In addition to 3.5% of the epimeric alcohol. [e] In addition to 10% *trans*-decal-1-one and 16% *trans*-decal-2-one.

pregnation using a volatile solvent. A stream of ozone was then passed through the silica gel containing ~1% by weight of the hydrocarbon at −78° [6] until it became saturated with ozone. It was then allowed to warm slowly, during ~0.5 hr, to room temperature, followed by elution of the organic material.

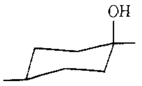
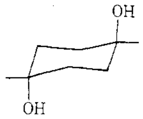
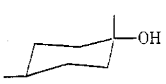
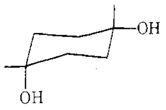
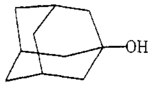
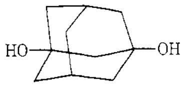
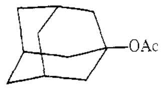
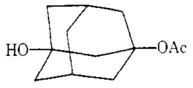
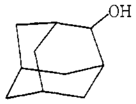
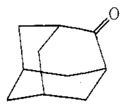
Using these reaction conditions, we have observed almost quantitative conversions of the hydrocarbons, resulting in a very high yield of the tertiary alcohols and an almost complete retention of configuration in the case of *cis*-decalin and the two isomeric *cis*- and *trans*-1,4-dimethylcyclohexanes (Table I).[5]

Thus the advantage of the dry ozonation is not only the almost quantitative conversions, but also practically exclusive formation of monooxygenated products. The alternative sweeping of hydrocarbon solutions with ozone for long periods of time may lead to reoxidation of the primarily formed products resulting in mixtures of polyoxygenated compounds as well as formation of impurities caused by oxidation of the solvent.[1,7]

The efficacy of the dry ozonation as a general method for stepwise hydroxylation of tertiary carbon atoms may be exemplified by hydroxylation of adamantan-1-ol, its acetate, and the two isomeric *cis*- and *trans*-1,4-dimethylcyclohexanols (Table II).

Under the same conditions secondary alcohols are oxidized to ketones as shown by a quantitative conversion of adamantan-2-ol to adamantanone.

Table II
Reaction of Substituted Hydrocarbons with Ozone on Silica Gel

Substrate	Product	Yield,[a] %	Conversion,[a] %
		>99.5	95
		76[b]	97
		99	43
		86	50
		>99.5	>99.5

[a] Based on the starting material consumed. [b] In addition to 5% of the trans diol.

We suggest that the mechanism of ozonation of saturated compounds in the adsorbed phase is the same as the one proposed by us for ozonation in solution.[2]

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References and Notes

(1) (a) J. R. Durland and H. Adkins, *J. Am. Chem. Soc.*, **61**, 429 (1939); (b) M. C. Whiting, A. Z. N. Bolt, and J. H. Parish, *Adv. Chem. Ser.*, **77**, 4 (1968); (c) G. A. Hamilton, B. S. Ribner, and T. M. Hellman, *ibid.*, **77**, 15 (1968); (d) C. C. Schubert and R. N. Pease, *J. Am. Chem. Soc.*, **78**, 2044 (1956); (e) D. G. Williamson and R. J. Cvetanovic, *ibid.*, **92**, 2949 (1970); (f) T. M. Hellman and G. A. Hamilton, *ibid.*, **96**, 1530 (1974); (g) J. E. Batterbee and P. S. Bailey, *J. Org. Chem.*, **32**, 3899 (1967).

(2) H. Varkony, S. Pass, and Y. Mazur, *Chem. Commun.*, 437 (1974).

(3) Saturated solvents normally used in ozonolysis, like methyl acetate, ethyl acetate, methyl chloride, carbon tetrachloride, and trifluorochloromethane, were found to react with ozone even at low temperatures.

(4) G. A. Cook, A. D. Kiffer, C. V. Klumpp, A. H. Malik, and L. A. Spence, *Adv. Chem. Ser.*, **21**, 44 (1959).

(5) The hydrocarbons used were purified by conventional techniques; the liquid ones also by passing through an $AgNO_3$–HNO_3 alumina column [E. C. Murray and R. N. Keller, *J. Org. Chem.*, **34**, 2234 (1969)]. GLC analysis indicated in all compounds used <0.01% impurities.

(6) Below this temperature the concentration of ozone adsorbed on silica increases rapidly. However we want to warn that at temperatures below −112° ozone liquifies and there is a potential explosion danger when handling silica gel containing adsorbed ozone and organic material at temperatures lower than −100°

(7) W. H. Clingman, Jr., *Chem. Abstr.*, **53**, 3066*h* (1959); U.S. Patent 2,849,484 (1958).

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