Table I. Alkylation of Benzene with (S)-$CH_3CHOXCOOR$[a]

X	R	solvent[b]	reacn time, h	T, °C	% isol yield	$[\alpha]^{22}_D$,[c] deg
SO_2Cl	CH_3	benzene	3	20	70	+109.8[d]
SO_2Cl	CH_3	dichloro-benzene	6	20	51	+106.0
SO_2CH_3	CH_3	benzene	6	80	80	+105.7
SO_2CH_3	C_2H_5	benzene	6	40	76	+65.7[f]

[a] General reaction conditions: to 4.7 g (59.7 mmol) of benzene and 3.9 g (29.5 mmol) of $AlCl_3$ was added 15.3 mmol of (S)-$CH_3CHOXCOOR$ [X = SO_2Cl, R = CH_3, $[\alpha]^{25}_D$ -81.44 ($CHCl_3$, c 1); X = SO_2CH_3, R = C_2H_5, $[\alpha]^{22}_D$ -53.0 ($CHCl_3$, c 1); X = SO_2CH_3, R = CH_3, $[\alpha]^{25}_D$ -56.4° ($CHCl_3$, c 1)] dropwise at 10 °C, and the mixture was stirred for 3-6 h at the reported temperature; at the end, the mixture was quenched at 0 °C with HCl (10%) and extracted with diethyl ether; the organic phase was neutralized, dried over anhydrous Na_2SO_4, and concentrated at reduced pressure, and the residue was purified by chromatography (silica gel, 70-230 mesh, 96/4 eluent heptane/diethyl ether). [b] No yield or a very low one was obtained with solvents CH_2Cl_2, CH_2ClCH_2Cl, CH_3NO_2, $C_6H_5NO_2$; on the contrary, hexane works well giving the same result as dichlorobenzene. [c] In toluene maximum specific rotations reported for (S)-methyl 2-phenylpropionate and (S)-ethyl 2-phenylpropionate are $[\alpha]^{22}_D$ +109.2° (toluene, c 6.2) and $[\alpha]^{24}_D$ +72.0° (toluene, c 10), respectively.[6] [d] A sample, after hydrolysis with HCl, gave the corresponding acid having specific rotation $[\alpha]^{22}_D$ +92.2° (benzene, c 3) [maximum specific rotation reported for (S)-2-phenylpropionic acid is $[\alpha]^{22}_D$ +95.1° (benzene, c 3.1)].[6] [e] In this case, 1.5 g (18.7 mmol) benzene in 8 mL of solvent was used. [f] $[\alpha]_D$ measured at 24 °C.

slowing down the alkylation reaction rate by dilution with an inert solvent as dichlorobenzene or hexane, or working at higher temperature, or changing the leaving group, we have obtained about the same stereospecificity. In a further experiment, working at 40 °C and stopping the reaction at about 50% conversion, we recovered, as expected, methyl 2-(mesyloxy)propionate of undiminished optical purity. Our results do not compare to what Suga and co-workers have previously reported[1h] in the alkylation of benzene with optically active 3-chlorobutanoic acid derivatives. The alkylation of benzene did not take place and the starting alkylating reagent was recovered without racemization when they used $AlCl_3$ equimolar to the chloro derivative; when a 20% molar excess of the Lewis acid was present, the starting chloride racemized to a considerable extent as alkylation reaction proceeded.[1h]

In view of the ready availability of optically pure lactic acid derivatives, the above synthesis should be of general utility in preparing optically active compounds of type $CH_3C^*H(Ar)Y$ when nonracemizing reaction conditions are used to elaborate the phenyl ring or the COOR group.

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The Trimethylsilyl Cationic Species as a Bulky Proton. Application to Chemoselective Dioxolanation

Summary: Use of the "bulky proton" containing reagents trimethylsilyl trifluoromethanesulfonate and 1,2-bis[(trimethylsilyl)oxy]ethane to ketalize or acetalize compounds containing two nonconjugated carbonyl groups or one nonconjugated and one α,β-unsaturated carbonyl group provides, with high selectivity, monodioxolanes bearing the ketal or acetal function at the less sterically hindered site.

Sir: Trialkylsilyl groups have been referred to as "super protons" when bonded to carbon and as "feeble protons" when attached to oxygen.[1] The properties of silicon from which these names arise have found extensive use in organic reactions during the past decade.[1,2] Herein, we introduce the concept and provide evidence that the trimethylsilyl cationic species (Me_3Si^+) can serve as a "bulky proton".

Dioxolanation is one of the most frequently used protective techniques in organic chemistry. Moreover, reagents capable of selectively protecting one carbonyl group in a di- or polyketone should be highly beneficial to the synthetic community. We have considered the possibility of differentiating two carbonyl groups by taking advantage of differences in their steric environments. Since most dioxolanations are catalyzed by acids,[3] the use of a catalyst containing a special moiety that is equivalent to a proton, but much bulkier, might provide the desired selectivity. The superacid,[4] trimethylsilyl trifluoromethanesulfonate[5] (Me_3SiOTf) with its bulky cationic trimethylsilyl moiety is a likely candidate for such a catalyst. In fact, Noyori et al. have reported an efficient ketalization procedure involving 1,2-bis[(trimethylsilyl)oxy]ethane (BTSE) and Me_3SiOTf as reagents.[6] The elegant idea of shifting the equilibrium of the reaction toward the products by forming the very stable hexamethyldisiloxane results in excellent yields of ketals at low temperature with simple ketones. Thus, this seemed to be an ideal system with which to test our bulky proton concept, especially since the reagent BTSE also contains cationic trimethylsilyl groups in place of the hydroxyl protons of ethylene glycol.

Treatment of 5α-pregnane-3,20-dione (**1**) with BTSE and a catalytic amount of Me_3SiOTf (see Table I) in CH_2Cl_2 at -78 °C provided the corresponding 3-ethylene ketal (**2**, 94%)[7] exclusively. Under similar conditions, 5α-androstane-3,17-dione (**3**) gave 3-ethylene ketal **4**[7] as the major product (96%), plus a trace of the corresponding diketal. In neither case was monoketalization at the more sterically hindered carbonyl group observed.

For compounds containing both nonconjugated and α,β-unsaturated carbonyl groups, monoketalization under

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(3) (a) Greene, T. W. "Protective Groups in Organic Synthesis;" John Wiley and Sons: New York, 1981; p 116. (b) Loewenthal, H. J. E. "Protective Groups in Organic Chemistry;" McOmie, J. F. W., Ed.; Plenum Press: New York, 1973; p 323.
(4) (a) Noyori, R.; Murata, S.; Suzuki, M. *Tetrahedron* **1981**, *37*, 3899. (b) Marsmann, H. C.; Horn, H.-G. *Z. Naturforsch. B* **1972**, *27*, 1448.
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(6) Tsunoda, T.; Suzuki, M.; Noyori, R. *Tetrahedron Lett.* **1980**, *21*, 1357.
(7) Vorbrüggen, H. *Steroids* **1963**, *1*, 45.

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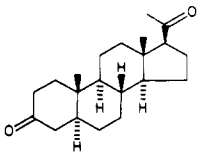
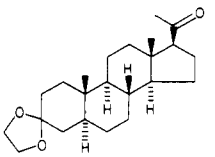
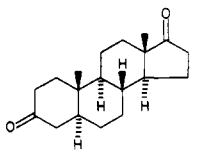
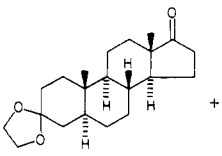
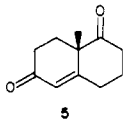
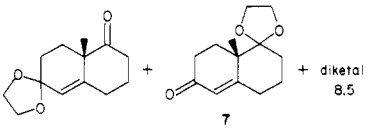
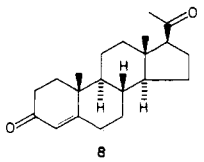
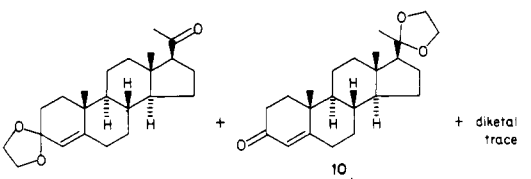
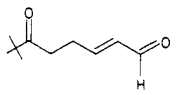
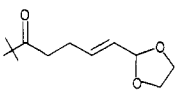
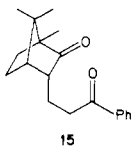
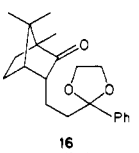
Table I. Chemoselective Dioxolanation with Bulky Proton (Me_3Si^+) Containing Reagents

substrate	$OSiMe_3$ $OSiMe_3$, equiv	Me_3SiOTf, equiv	concentration, M substrate/CH_2Cl_2	time, (h)/ temp, °C	products, %[a] (%)[b]	selectivity[c]
 1	0.98	0.02	0.21	6/−78	 2 100 (94)	100:0
 3	0.98	0.02	0.61	6/−78	 + diketal trace 4 99 (96)	99:0
 5	1.05	0.02	1.5	51/−78	 + diketal 8.5 6 77 (65) 7 2.9	27:1
 8	1.2	0.03	0.63	33/−78	 + diketal trace 9 67[d] 10 25[d]	2.7:1
 13	1.05	0.02	0.61	5/−78	 14 96 (91)	96:0
 15	1.15	0.25	0.60	31/−45	 16 89 (82)	89:0

[a] GC yield. [b] Isolated yield. [c] Selectivity is between isomeric monoketals; diketal is not included. [d] Yields are based on 30% conversion of substrate.

typical conditions (ethylene glycol + acid with the removal of water) occurs at the nonconjugated carbonyl group[8] unless the pH of the solution is carefully controlled.[9] In the Wieland–Miescher ketone (**5**), the steric congestion about the α,β-unsaturated carbonyl group at C-3 is significantly less than that about the nonconjugated C-9 carbonyl group. Therefore, this compound is an excellent model for demonstrating the usefulness of the bulky proton in selective ketalization.[10] Reaction of **5** with BTSE (1.05 equiv) in the presence of Me_3SiOTf (0.02 equiv) at −78 °C in CH_2Cl_2 gave a mixture of 3-ethylene ketal **6**[9b] (77%), 9-ethylene ketal **7**[8] (2.9%), and the corresponding diketal (8.5%). The ratio of **6**:**7** was 27:1. Interestingly, the double bond remained at the Δ^4 position in **6** and the diketal. It should be noted that temperature plays an important role in this reaction. The ratio of **6**:**7** dropped to 5.1:1 when the reaction was carried out at ~−60 °C. Furthermore, no **6** could be detected when the reaction was begun at −78 °C and warmed to ~−10 °C for 8.5 h. Instead, only **7** (73%) and the diketal (6.3%) were obtained.

To prove that **7** is the more thermodynamically stable monoketal, we carried out the following experiment. A mixture of **6** and **5** in a 1:10 ratio was stirred with 0.18 equiv of Me_3SiOTf in CH_2Cl_2 at ~−10 °C for 3 h. The 3-ethylene ketal (**6**) completely disappeared and a 1:9 mixture of **7** and **5** was obtained. This efficient transketalization process also fully accounts for the absence of **6** during the dioxolanation of **5** at −78 ~ −10 °C. Evidently, compound **6** can be obtained only under conditions of kinetic control, i.e., at low temperature.

Two factors might possibly favor selective ketal formation at the enone center in **5**: (i) low acidity of the catalyst[9] and (ii) steric hindrance at C-9. Factor i was quickly excluded by the following model study. Treatment of a mixture of 3-methyl-2-cyclohexenone (**11**) and cyclohexanone (**12**) (1:1) with 0.5 equiv of BTSE (i.e., (**11** + **12**):BTSE = 2:1) and Me_3SiOTf (0.02 equiv) at −78 °C for

(8) Nitz, T. J.; Paquette, L. A. *Tetrahedron Lett.* **1984**, *25*, 3047 and references therein.

(9) (a) Herzog, H. L.; Jevnik, M. A.; Tully, M. E.; Hershberg, E. B. *J. Am. Chem. Soc.* **1953**, *75*, 4425. (b) De Leeuw, J. W.; De Waard, E. R.; Beetz, T.; Huisman, H. O. *Recl. Trav. Chim. Pays-Bas* **1973**, *92*, 1047.

(10) A clever approach to this problem using a hindered collidinium salt as catalyst has been reported by Nitz and Paquette, see ref 8.

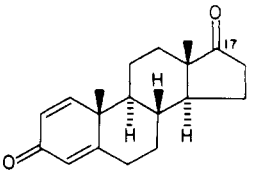
4 h generated two ketals. The ratio of (conversion of **11** to **11**-ethylene ketal)/(conversion of **12** to **12**-ethylene ketal) was 1:7.3. This example indicates that, in the absence of steric bias, nonconjugated carbonyl groups are ketalized much faster than α,β-unsaturated ketones by the reagents Me_3SiOTf/BTSE. Also, Me_3SiOTf is generally regarded as a strong aprotic acid.[4b] Therefore, selective ketalization of the enone moiety in **5** must not be due to the acidity of the catalyst but to the other factor—steric hindrance.

The trimethylsilyl cationic species can also bias a less congested enone moiety vs. a more hindered acetyl functionality. Thus, reaction of progesterone (**8**) and BTSE (1.2 equiv) with a catalytic amount (0.03 equiv) of Me_3SiOTf afforded the isomeric ketals **9**[11] and **10**,[11] plus a small amount of diketal. The ratio of **9**:**10** obtained with the Me_3SiOTf/BTSE system (2.7:1) was remarkably different from that obtained with an H^+/ethylene glycol system (1:3.5).[11] However, this Me_3Si^+-catalyzed reaction proceeded very slowly at −78 °C. Raising the temperature to −60 °C in an attempt to accelerate the reaction gave lower selectivity (1:1). Addition of more Me_3SiOTf (0.10 equiv) did not change the reaction rate significantly.

Excellent selectivity was observed with two additional dicarbonyl substrates. Thus, when 7,7-dimethyl-6-oxo-2-octenal (**13**) was stirred with BTSE (1.05 equiv) and Me_3SiOTf (0.02 equiv) at −78 °C for 5 h, acetal **14** was obtained as the only major product (91%). The corresponding ketal could not be detected.[12] To our knowledge, this is the first example of acetalization of an α,β-unsaturated aldehyde with BTSE and Me_3SiOTf.

Selective protection of a benzylic ketone function in the presence of a nonconjugated ketone group was also achieved. Treatment of **15** with BTSE (1.15 equiv) and Me_3SiOTf (0.25 equiv) in CH_2Cl_2 at ~−45 °C for 31 h gave **16**[13] in 82% yield. The monodioxolane that would have resulted from reaction of BTSE with the nonconjugated carbonyl group in **15** could not be detected in the reaction mixture.[14] Substrate **15** did not react with BTSE and Me_3SiOTf at −78 °C in CH_2Cl_2.

We have also found that the cross-conjugated dienone moiety is inactive toward Me_3SiOTf/BTSE. Under the same conditions used for the other substrates, no reaction occurred with 1,4-androstadiene-3,17-dione (**17**) at −78 °C



17

in 26 h. Comparing this result with that obtained for substrate **3**, it surprises us that the C-17 carbonyl group in **17** is inert. This may be due to a conformational transmission effect. Such effects are well-known to occur in steroids.[15]

In conclusion, the role of Me_3Si^+ in dioxolanation is similar to that of H^+. However, the bulkiness of Me_3Si^+ allows it to differentiate between carbonyl groups on the basis of steric hindrance. Our evidence confirms that Me_3Si^+ can be regarded as a bulky proton. Its unique properties with regard to chemoselectivity possess synthetic value.

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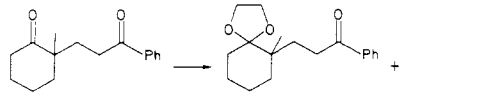
(11) Brown, J. J.; Lenhard, R. H.; Bernstein, S. *J. Am. Chem. Soc.* **1964**, *86*, 2183. ^1H NMR ($CDCl_3$) of **9**: δ 5.23 (br s, 1 H), 3.97 (m, 4 H), 2.11 (s, 3 H), 2.67–0.74 (m, 20 H), 1.03 (s, 3 H), 0.63 (s, 3 H).

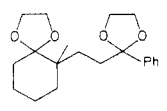
(12) In the absence of significant steric bias, a nonconjugated ketone is dioxolanated more rapidly than an α,β-unsaturated aldehyde with BTSE and Me_3SiOTf; see: Leu, L.-C.; Robl, J. A.; Wetzel, J. M.; Hwu, J. R., submitted for publication. ^1H NMR ($CDCl_3$) of **14**: δ 5.96 (dt, *J* = 15.3, 6.0 Hz, 1 H), 5.49 (dd, *J* = 15.3, 6.0 Hz, 1 H), 5.17 (d, *J* = 6.0 Hz, 1 H), 3.93 (m, 4 H), 2.70–2.10 (m, 4 H), 1.13 (s, 9 H).

(13) ^1H NMR of **16** ($CDCl_3$): δ 7.40–7.23 (m, 5 H), 4.10–3.63 (m, 4 H), 2.35–1.02 (m, 10 H), 0.88 (s, 3 H), 0.85 (s, 3 H), 0.76 (s, 3 H).

(14) As in the case of α,β-unsaturated aldehydes, significant steric bias is required in order to selectively dioxolanize a benzylic ketone moiety in the presence of a nonconjugated ketone group with bulky proton containing reagents. E.g., **18** with BTSE (0.98 equiv) and Me_3SiOTf (0.09 equiv) in CH_2Cl_2 at −78 °C for 78 h gave **19** as the only monodioxolane product (68%), along with diketal **20** (30%).



18 **19**



20

(15) (a) Barton, D. H. R.; Head, A. J.; May, P. J. *J. Chem. Soc.* **1957**, 935. (b) Eliel, E. L.; Allinger, N. L.; Angyal, S. J.; Morrison, G. A. "Conformational Analysis;" Interscience; reprinted by the American Chemical Society: Washington, DC, 1981; p 345.

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Enantiospecific Total Synthesis of (−)-Swainsonine: New Applications of Sodium Borohydride Reduction

Summary: A short, enantiospecific synthesis of (−)-swainsonine (**1**) from D-mannose has been achieved by a route involving, as a key step, a double cyclization of **4c**. The synthesis takes advantage of new features of sodium borohydride for reducing conjugated esters and lactams.

Sir: Swainsonine (**1**) is a representative of the class of polyhydroxylated indolizidine alkaloids which inhibit the biosynthesis of oligosaccharides through their glycosidase inhibitory activities.[1-3] It has recently been found that

(1) Isolation: (a) Colegate, S. M.; Dorling, P. R.; Huxtable, C. R. *Aust. J. Chem.* **1979**, *32*, 2257. (b) Malyneux, R. J.; James, L. F. *Science (Washington, D.C.)* **1982**, *216*, 190. (c) Schneider, M. J.; Ungermach, F. S.; Broquist, H. P.; Harris, T. M. *Tetrahedron* **1982**, *39*, 29.

(2) Activity: (a) Elbein, A. D.; Solf, R.; Dorling, P. R.; Vosbeck, K. *Proc. Natl. Acad. Sci. USA* **1981**, *78*, 7393. (b) Tulsiani, D. R. P.; Harris, T. M.; Touster, O. *J. Biol. Chem.* **1982**, *257*, 7936. (c) Chotai, K.; Jennings, C.; Winchester, B.; Dorling, P. R. *J. Cell Biochem.* **1983**, *21*, 107. (d) Greenaway, V. A.; Jessup, W.; Dean, R. T.; Dorling, P. R. *Biochem. Biophys. Acta* **1983**, *762*, 569. (e) Winkler, J. R.; Segal, H. L. *J. Biol. Chem.* **1984**, *259*, 1958.

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