A new lactone synthesis[15] proved effective for the conversion of diiodide **4c** to bakkenolide A—viz., the methyl acrylate derivative **5** in DME at −58 °C on successive treatment with 1.0 equiv of lithium bis(trimethylsilyl)-amide in DME, 0.9 equiv of the diiodide in HMPA, and then once again with 1.0 equiv of the amide base furnished directly in 69% yield hydrindane **6** as a ca. 3:1 mixture (NMR) of C-7 epimers.[16] Deprotection–lactonization of **6** occurred on brief contact with aqueous hydrofluoric acid in acetonitrile[17] to produce in essentially quantitative yield the corresponding spiro β-methylene-γ-butyrolactones, from which pure racemic bakkenolide A (**1**),[10] mp 47–48 °C, was readily obtained by crystallization from cold pentane. This material was indistinguishable spectroscopically (IR, NMR, MS) and chromatographically (TLC, VPC) from an authentic sample of the natural product.

Work directed at extending this efficient approach to the synthesis of other bakkanes is planned.

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Alkylation of Aromatic Compounds with Optically Active Lactic Acid Derivatives: Synthesis of Optically Pure 2-Arylpropionic Acid and Esters

Summary: The alkylation of benzene with (*S*)-methyl 2-[(chlorosulfonyl)oxy]- or 2-(mesyloxy)propionate, in the presence of aluminum chloride, affords (*S*)-methyl 2-phenylpropionate in good chemical (50–80%) and excellent optical yield (≥97% as determined by rotation), with inversion of configuration at the attacking carbon atom.

Sir: Generally Friedel–Crafts alkylation proceeds with a high degree of racemization (40–100%) when an optically active alkylating reagent is used.[1] When an optically active product is recovered, a partial inversion of configuration, as a normal result, is observed. Some examples of highly stereospecific reactions have, however, been reported such as the alkylation of benzene with (*R*)-1,2-epoxypropane and (*R*)-1,2-epoxybutane (optical yield ~ 100% with inversion of configuration)[2a,b] and with (*R*)-2-chloro-1-phenylpropane (o.y. ~ 96% with retention of configuration).[2c] These results have been explained on the basis of the cyclic nature of the alkylating reagents or as the result of the formation of cyclic intermediates. When a low stereospecificity in this type of reaction is found, it may be due either to the formation of a free carbonium ion intermediate or to the racemization of the starting material[1h] and/or of the final product.[3,4]

Here we report the first example of a Friedel–Crafts alkylation reaction, using acyclic alkylating reagents, that proceeds with high stereospecificity (≥97%, Table I) and inversion of configuration. The reaction conditions are similar to procedures reported in patents[5a,b] where racemic reagents have been used.

It is of note that the alkylation reaction also works in the presence of basic inorganic and organic compounds such as calcium carbonate, pyridine, poly(vinylpyridine), or imidazole, giving the same optical yields but lower chemical yields. Exploratory experiments with different Lewis acids gave no improvement or low yields.

When we tried to extend this reaction to other aromatic substrates such as toluene, isobutylbenzene, tetralin, anisole, naphthalene, 2-methoxynaphthalene, we obtained mixtures of isomeric alkylation products and/or byproducts. At the present, we are unable to improve the reaction as reported in some patterns.[5c–h] However, after careful purification, by flash chromatography (eluent 7/3 hexane/ethyl acetate), of the mixture obtained in the reaction of isobutylbenzene and optically pure (*S*)-2-(mesyloxy)propionic acid, a sample of (*S*)-2-(4-isobutylphenyl)propionic acid (Ibuprofen) having $[\alpha]^{25}_D$ +58.5° (ethanol 95%, *c* 2) [maximum specific rotation reported $[\alpha]^{25}_D$ +60° (ethanol 95%, *c* 2)][7] was recovered.

Concerning the mechanism, it is reasonable to think that cyclic intermediates are involved in which the COOR and OX groups strongly coordinate with aluminum, though it cannot, at present, be established which atoms are actually bonded. Benzene is expected to attack the chiral carbon atom from the backside of the leaving group, analogously to what has been previously reported.[1d–l,2a,b] No free Lewis acid should be present to racemize the starting material, even if a molar ratio of Lewis acid to ester of 2 is used (compare ref 1h) and/or the rate of the alkylation should be appreciably faster than the scrambling of the OX group. The latter hypothesis is, in our opinion, less probable since

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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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