Addressing the regioselectivity problem in organic synthesis

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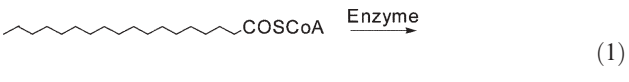
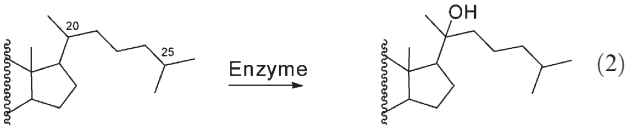
A screening process uncovered a heterogeneous catalytic system that hydrolyzes one of two nearly identical ketals in several diketals with a high selectivity.

Organic synthesis is winning the war against its challenges. The reactions available to the synthetic organic chemist number in the countless thousands. Natural products with over sixty chiral centers have been constructed.[1] Chiral catalysts and auxiliaries giving enantiomeric excesses greater than 90% abound.[2] We hear occasionally that, "If you can draw it, you can make it." Although this statement is no doubt hyperbole, it does serve to drive home the impressive successes in the field of organic synthesis. Nevertheless, there remains a major problem in organic synthesis that has not been solved. In fact, it has only rarely been addressed: enzyme-like regioselectivity.

We define "enzyme-like regioselectivity" as the ability to distinguish between two functionalities in a molecule that (a) are positionally distinct but otherwise virtually identical in their steric/electronic environments; (b) are often located in quite different parts of the molecule; and (c) are not affected by an intramolecular catalysis that favors one of the functionalities. Chemists confronted with two such groups are often unable to operate selectively upon only one of them. For example, 3,6-diketodecane has never, to our knowledge, been selectively mono-reduced. Enzymes, on the other hand, are well known to react exclusively on the basis of location alone.[3] For example, stearyl CoA is regiospecifically dehydrogenated at the 9-position by the enzyme acyl CoA desaturase (eqn (1))[4] while the initial step in the conversion of cholesterol to pregnenalone involves a regiospecific oxidation at the tertiary C-20 carbon, with the nearby tertiary C-25 carbon remaining untouched (eqn (2)).[5] No chemist nowadays could duplicate these feats non-enzymatically, and hence the challenge.[6]



(1)

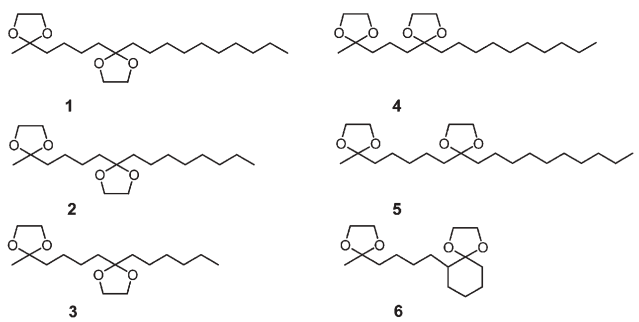


(2)

Regioselectivity, like diastereo- and enantioselectivity, is of course commonplace in organic chemistry. For example, toluene is nitrated faster at the *para* position than at the *ortho* and *meta* positions. An aldehyde can be reduced in the presence of an unhindered ketone.[7] One can regioselectively cleave the C–N bond to the tertiary amine of $RCH(NHR)(NR_2)$.[8] In a stannylene derivative of a diol, one oxygen is acylated faster than the other.[9] However, our definition of "enzyme-like regioselectivity" does not encompass such cases because they arise mainly from inherent reactivity and steric differences. Examples of true enzyme-like regioselectivity are rather uncommon and would include the epoxidation of squalene's terminal double bond in preference to its other identically substituted double bonds.[10]

How do enzymes accomplish their remarkable regioselectivity? A key factor lies in the binding of substrates to the enzyme prior to reaction. Binding processes place only one of two nearly identical substrate functionalities at the enzyme's catalytic site, thereby providing the necessary selectivity. Those wishing to emulate this action must, therefore, construct a catalytic surface with specific binding properties. One might conceivably do so by designing catalytic host molecules that can discriminate between nearly identical reactive groups in a guest (similar to enzyme action).[11–15] But chemistry has not yet acquired an understanding of intermolecular forces sufficient to predict the precise geometry of most substrate/surface interactions. Consequently, synthesis of such a host is a costly and chancy enterprise. We have, therefore, adopted a screening program similar to that used in the discovery of many enantioselective catalysts. A main difference is that we searched for selectivity between two distant, non-interacting functionalities rather than selectivity at a single locus.

The reaction in question involved initially the selective hydrolysis of only one of the two ketal groups in compound **1** of Scheme 1. Sterically and electronically the two ketal groups are nearly identical because both of them are positioned at secondary carbons in a saturated chain. Although the 2-ketal might be considered more "exposed" than the 7-ketal, an inherent reactivity difference (if such exists) was insufficient to achieve useful selectivity with several classical homogeneous and heterogeneous catalysts that were tested *via* literature procedures: pyridinium *p*-toluenesulfonate (methanol, acetone, acetonitrile or hexane);[16] $CeCl_3 \cdot 7H_2O$, NaI (methanol or acetonitrile);[17]



Scheme 1 Diketals examined in this work.

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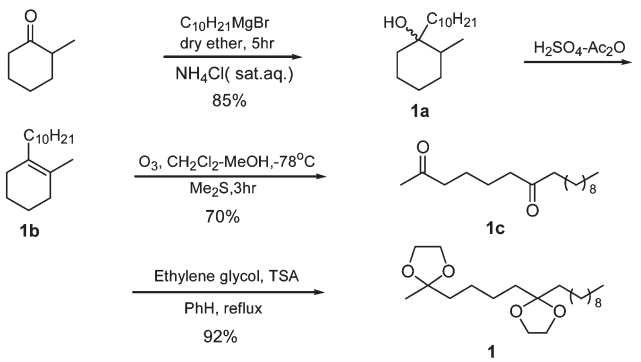
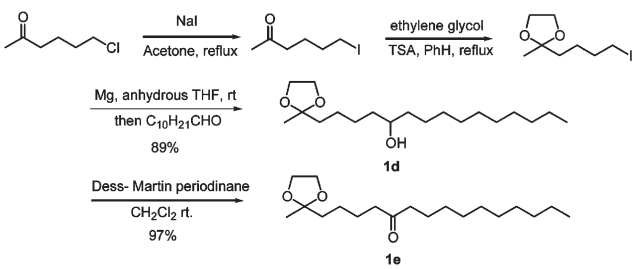
poly(4-vinylpyridinium *p*-toluenesulfonate) (methanol); oxalic acid (methanol);[18] $TiCl_4$ (diethyl ether);[19] HCl (acetone);[20] AcOH (acetone);[21] $PdCl_2$ (acetone);[22] AlI_3 (acetonitrile);[23] Ph_3CBF_4 (dichloromethane);[24] and $Er(OTf)_3$ (acetonitrile).[25] During our screening, however, we did find one useful heterogeneous catalyst that greatly favored deprotection of one ketone over the other: $MgSO_4$ in wet hydrocarbon solvents.[26] A remarkable regioselective preference for hydrolysis of the 2-ketal was evident as will be described following the relevant experimental details below.

Diketal **1** itself was synthesized by adding *n*-$C_{10}H_{21}MgBr$ to 2-methylcyclohexanone and dehydrating the resulting tertiary alcohol to give 1-decyl-2-methylcyclohexene (Scheme 2). Ozonolysis of the olefin followed by a dimethyl sulfide workup gave 2,7,-diketoheptadecane from which the diketal was readily prepared and identified spectroscopically (NMR and MS) and by elemental analysis. Analogs of **1**, mentioned below, were synthesized in a like manner. Diketal **1** was "mono-hydrolyzed" as follows: in a 4 mL glass vial was added 2 mg of **1** in 2 mL wet hexanes (prepared by repeatedly shaking hexanes with purified water), 200 mg magnesium sulfate powder (EMD Chemicals, Inc., freshly opened), and a micro magnetic stirring bar. After stirring for a measured time at room temperature, 100 μL were withdrawn, filtered through a 0.2 μm-pore membrane, and injected into an HPLC (C-18 reverse-phase column; methanol–water (85%/15%) eluent; evaporative light scattering detector). Identifying the two monoketone peaks HPLC peaks required the synthesis of the 7-monoketone compound (Scheme 3): 6-chloro-2-hexaone was converted into the iodide derivative with NaI/acetone and then treated with ethylene glycol/TSA in benzene. The resulting ketal was reacted with Mg in THF to make the Grignard that was added to undecylic aldehyde to give the 2-ketal-7-hydroxyheptadecane. A Dess–Martin oxidation of the secondary alcohol yielded the desired 7-monoketone that has an HPLC retention time



Scheme 2 Synthesis of diketal **1**.



Scheme 3 Synthesis of the 7-monoketone corresponding to **1**.

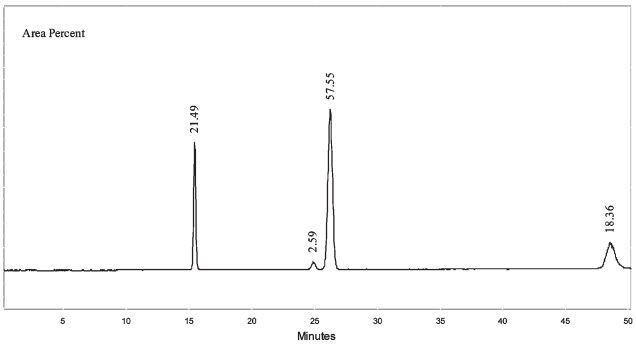


Fig. 1 HPLC of the reaction between diketal **1** and $MgSO_4$ in wet hexanes at room temperature at 24 h. The peaks (in order of appearance) are diketone, 7-monoketone, 2-monoketone and diketal.

identical to that of the earlier-emerging peak of the two monoketone product peaks from the $MgSO_4$-catalyzed hydrolysis.

A reaction of **1** with $MgSO_4$ in wet hexanes after 24 h gave the HPLC shown in Fig. 1. The mixture contained (in increasing order of retention time) 21% diketone; 3% 7-monoketone; 58% 2-monoketone; and 18% diketal. Accordingly, the preference for 2-ketal hydrolysis over 7-ketal hydrolysis is 19 : 1. A repeat gave 70% 2-monoketone (typical of the experimental uncertainty). These numbers were affirmed by two different experimenters. The selective hydrolyses proceeded as well in wet benzene as in wet hexanes, but wet ethyl acetate, chloroform and acetonitrile gave no reaction. Nor was a reaction observed with a smaller amount (50 mg) of $MgSO_4$ or $MgCl_2$ in wet benzene.

With these results in hand, the question came up, of course, as to the regioselectivity with structural analogs of **1** and, as such, we examined five additional diketals (Scheme 1). The HPLC data for these $MgSO_4$-catalyzed hydrolyses are given in Table 1. It can be seen from the sixth column that very high regioselectivities (ranging from 23 : 1 to >95 : 1) are also possible with these analogs. The reasons for these regioselectivities are at the moment obscure, but they seem almost certainly related to selective binding of the diketals to the $MgSO_4$ surface.

A key observation helped clarify the catalytic mechanism: The ketals of 2- and 7-heptadecanone were hydrolyzed only very slowly under our conditions (0–3% product after 24 h). We surmise that effective binding to the $MgSO_4$ interface requires chelation to two ketals within the same molecule, after which only one is hydrolyzed. Thereupon, the reactant dissociates from the $MgSO_4$ surface, leading to the production of mainly mono-hydrolyzed

Table 1 HPLC-Determined percentages of compounds in the deprotection reaction with $MgSO_4$ in wet hexanes after 24 h at room temperature

Compound	Diketone	(6, 7 or 8)-monoketone	2-Monoketone	Diketal	2-Monoketone/(6, 7 or 8)-monoketone
1	21	3	58	18	19 : 1
2	14	1	60	25	60 : 1
3	0	0	18[a]	82	>95 : 1
4	10	1	46	43	46 : 1
5	47	2	45	6	23 : 1
6	0	0	20[a]	80	>95 : 1

[a] Little change was observed in another 24 h.

product. It is suggested, therefore, that regioselectivity is predicated upon tight bidentate binding of the reactant followed by loose or non-existent monodentate binding of the product. The fact that bis-hydrolysis product was observed (Table 1) implies that it was formed prior to dissociation of the mono-product from the catalyst surface.

An ability to operate on only one of two nearly identical,[27] distant functional groups constitutes a synthetically important technology. Our results in this field are encouraging but only an initial confrontation with the problem. Thus, the presence of double-hydrolyses limits the overall yield of the major mono-ketone. Yet our data constitute a feasibility study that should encourage further research into "surface-imposed regioselectivity". It is to be hoped that with the appropriately designed catalysts, molecular position, rather than classical stereoelectronic factors, will someday play a bigger role in dictating the outcome of synthetic reactions.

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27 Transforming only one of two identical groups is in fact an easier problem than transforming only one of two nearly identical groups because in the former case reaction at either site can give specificity.