Natural-Product Modification

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Site-Selective Derivatization and Remodeling of Erythromycin A by Using Simple Peptide-Based Chiral Catalysts**

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Medicinal chemistry relies on the efficient generation of analogs of lead compounds. Natural products represent a special class of leads since they have survived eons of natural selection and generally evolved to perform a specific function.[1] Yet, natural products are difficult to modify efficiently

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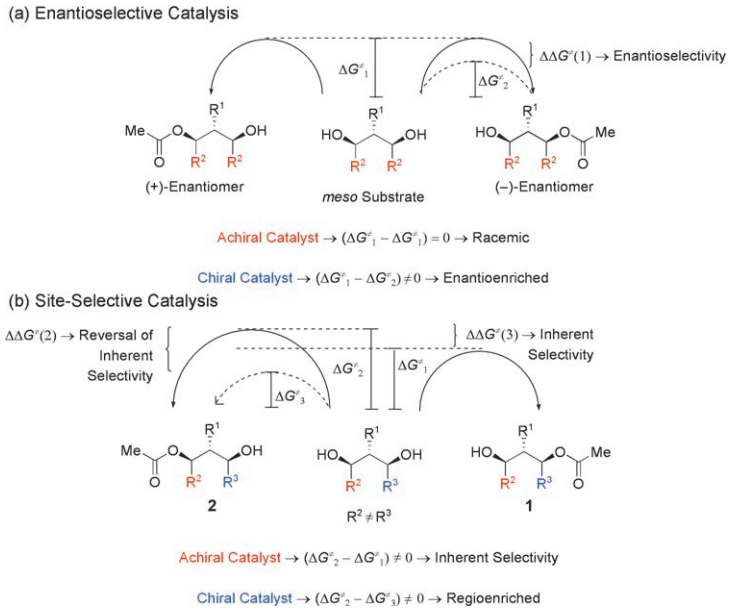
by chemical methods because of their complexity and multifunctional nature.[2] Enzymatic catalysts have been applied in this context.[3] However, the range of reactions that may be employed, and the specificities they exhibit, often lead to a limited set of natural-product analogs. Using peptide-based catalysts, we report herein unique examples of small-molecule, chiral catalyst-dependent, site-selective modifications of a natural product polyol, erythromycin A.

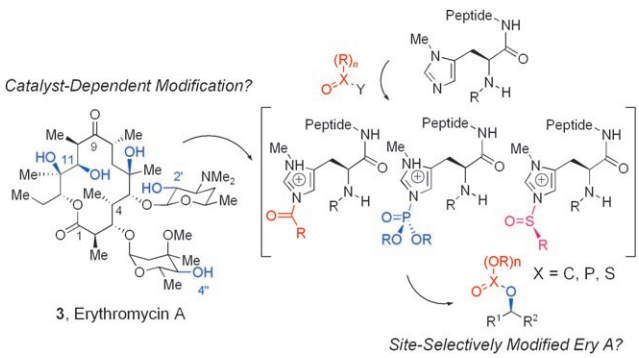
The selective derivatization of polyols is a special challenge to asymmetric catalysis. Unlike enantioselective catalysis, wherein competing reaction pathways present equivalent activation barriers in the absence of a chiral catalyst (e.g., desymmetrization as shown in Scheme 1a), regioselective, "site-selective" catalysis presents the additional challenge of unequal reaction barriers (Scheme 1b). Thus, if a desired polyol derivative requires modification of a hydroxy group of lower inherent reactivity relative to others, then increased demands are placed on a chiral catalyst: the rate of functionalization at the desired, less reactive site must be sufficiently enhanced to overcome and surpass the inherent rate of the more reactive site in order to achieve a selective reaction (i.e., $\Delta\Delta G^{\ddagger}(2) \gg \Delta\Delta G^{\ddagger}(3)$). For natural-product modification, the viability of any approach therefore requires that catalysts are able to affect reversals of the inherent reactivity of individual sites within the molecule. In this sense, the catalyst introduces an element of "double diastereodifferentiation," as catalyst architecture may enhance inherent reactivity in a "matched" sense.[4] Alternatively, in the case of a desired reversal of innate selectivity, one wishes to find powerful catalysts that are "mismatched," in order to fully overcome the native kinetic preference.



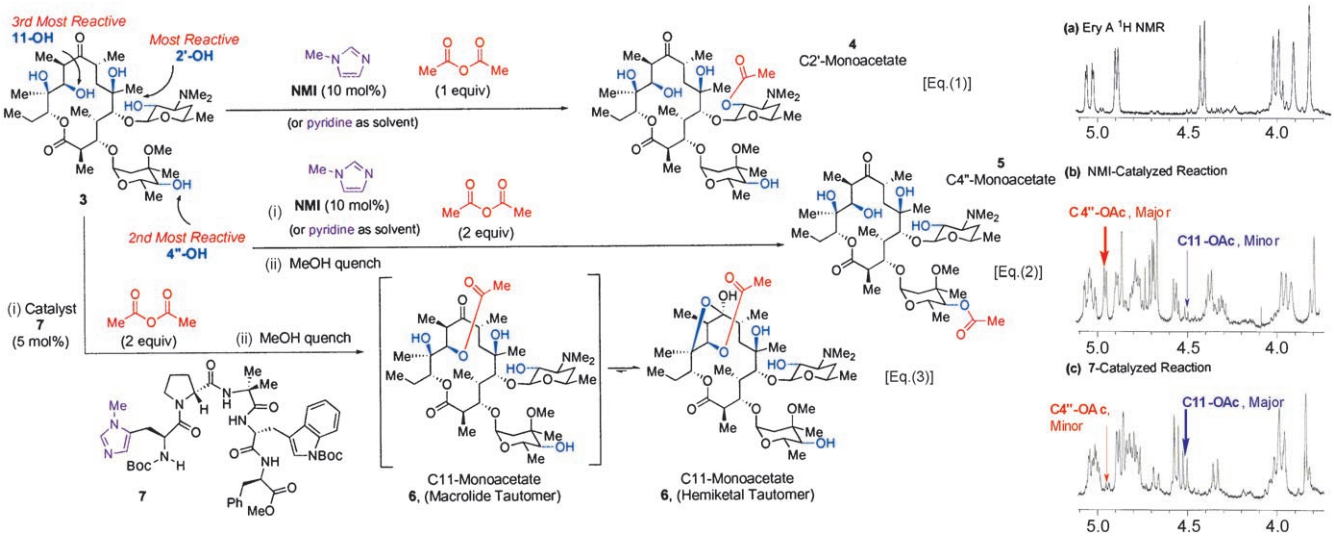
Scheme 1. a) Reaction coordinate for the enantioselective desymmetrization of a *meso* substrate. With an achiral catalyst, the two hydroxy groups react at equal rates. A chiral catalyst may accelerate one pathway leading to enantioselectivity. b) In a site-selective reaction, the two hydroxy groups are of unequal reactivity. Achiral catalysts lead to a product distribution that reflects the inherent reactivity of the two sites ($\Delta\Delta G^{\ddagger}(3)$; **1** is the major product). To form the product of functionalization at the least reactive site (**2**), $\Delta\Delta G^{\ddagger}(2)$ must be large to overcome the lower reactivity, and further favor the formation of the "minor" product.

As a prototype polyol for study of site-selective catalysis, we began with erythromycin A (**3**), an antibiotic with a storied history in both medicinal and synthetic chemistry.[5] We then chose to explore the fundamental process of alcohol acylation, a typical "group transfer" process that could lead to classes of analogs wherein hydroxy groups are converted to unique esters. We have reported that low molecular weight peptide-based catalysts are effective enantioselective catalysts for various group transfers, including acylation,[6] phosphorylation,[7] and sulfinylation.[8] The common chiral catalyst scaffold for group transfer is exemplified by nucleophilic, histidine-based catalysts as shown in Scheme 2.

We initially demonstrated that indeed, the hydroxy group array of **3** provides a range of relative reactivities. The reactivity hierarchy was initially established in the seminal report of Abbott Laboratories, employing pyridine as solvent and catalyst.[9] In our own studies, we found the Abbott results to be entirely reproducible. Furthermore, we established that the achiral catalyst *N*-methylimidazole (NMI) afforded similar results. Indeed, the C2′-hydroxy group undergoes acylation first, due in part to the autocatalytic vicinal tertiary amine, to give the 2′-monoacetate **4** as the major product when a limiting quantity of acetic anhydride (Ac_2O) is used (Equation (1) in Scheme 3). Indeed, this site undergoes acylation even in the absence of a catalyst. The next most reactive position is the C4″-hydroxy, as evidenced by preferential formation of the C2′,C4″-diacetate when NMI is used with additional Ac_2O; this diacetate is converted to C4″-monoacetate **5** when the reaction is quenched with MeOH, which autocatalytically cleaves the C2′-acetate group (Equation (2) in Scheme 3). Finally, the least reactive secondary site, the C11-OH, acylates such that an Ery A-triacetate (not shown) forms, but only after prolonged reaction time. The tertiary alcohols of **3** are substantially less reactive under these conditions. Under catalysis by NMI (10 mol%), or when pyridine is employed as solvent, the inherent selectivity for **5**/**6**



Scheme 2.



Scheme 3. Reactions of **3** and ^{1}H NMR spectra (400 MHz) of a) erythromycin A in a diagnostic ppm window, b) the unpurified reaction mixture when NMI is used as catalyst, and c) of the unpurified reaction mixture when peptide **7** is used as catalyst. Both spectra (b) and (c) are recorded prior to methanolysis. Boc = *tert*-butoxycarbonyl.

may be extracted to be approximately 4:1, although the ratio is strongly dependent on overall extent of conversion. It is notable that with NMI as catalyst, even after 3 days, < 30 % of **3** is converted to **5** and **6** (via **4**). Isolation of large quantities of **6** is therefore difficult.

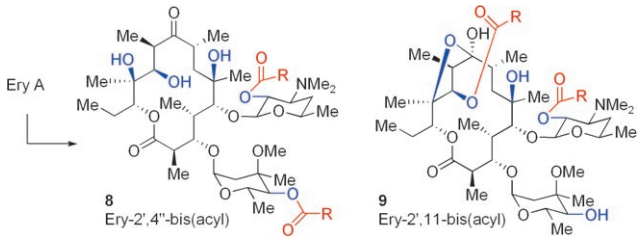
Our goal then became the identification of a small-molecule catalyst that would reverse the inherent reactivity such that the C11-OH group is modified preferentially over the more reactive C4″-OH of **3**. We examined 137 peptide catalyst candidates, chosen at random from our catalyst libraries. Shown in Scheme 3 are typical ^{1}H NMR spectra (400 MHz) of the reaction mixtures when Ac_2O is employed with different catalysts. Notably, many of the peptides examined exhibit NMI or pyridine-like behavior, favoring the C4″-monoacetate **5**, after MeOH quench (Scheme 3b). However, when peptides disposed toward the adoption of β-turn-like structures are employed (e.g., **7**),[10] a reversal of inherent selectivity is observed.[11] In addition, the peptide-catalyzed reactions are generally significantly faster than those promoted by pyridine or NMI. The major product formed under catalysis by **7**, following MeOH quench, is clearly the C11-derivative **6** (Scheme 3c and Equation (3)). We estimate by ^{1}H NMR integration that catalyst **7** delivers a ratio of **5**/**6** of ca. 1:5.[12]

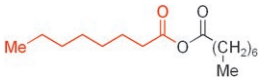
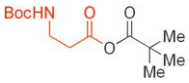
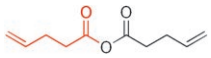
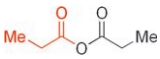
Notably, peptide **7** provides not only a catalyst-dependent derivatization of a unique, inherently less reactive hydroxy. In addition, C11-monoacetate **6** exists almost exclusively as its hemiketal tautomer. Everett and co-workers have rationalized hemiketalization of C11-acetate derivatives of erythromycin as a consequence of the loss of a macrolide-stabilizing hydrogen bond between the C11-OH and the C9-carbonyl in native erythromycin.[13] Independent of the structural basis of the tautomerization, the site-selective catalysis results in skeletal reorganization of the natural product.[14] Such reactions, wherein a chiral catalyst not only modifies a unique, inherently disfavored site, but also reorganizes the natural product structure, may be of particular value to the generation of diverse, natural product-derived compounds.

Catalyst **7** appears general for additional group transfers. For example, a dramatic reversal is observed with octanoyl anhydride, setting the stage for site-selective "lipidation" of natural products (Table 1, entry 1). Whereas reaction with pyridine delivers **8a**/**9a** with greater than 10:1 selectivity, catalyst **7** strongly reverses the selectivity such that **9a** is the major product with selectivity of 1:9. Transfer of the β-alanyl moiety via the mixed anhydride also provides a strong reversal (Table 1, entry 2). Achiral catalysts favor **8b** (5:1 over **9b**), while catalyst **7** delivers high selectivity for **9b** (1: > 10). The transfer of functionalized reagents implies the potential for selective labeling of natural products at specific sites. Selective transfer of an alkenyl group is illustrated in entry 3, wherein catalyst **7** reverses the inherent selectivity such that **9c** is the preferred product (5:1 selectivity, **9c**/**8c**). Smaller substrates appear to provide less drastic reversals. Propionyl transfer with achiral catalysts leads to modest selectivity for the inherently favored **8d** (2:1), whereas catalyst **7** favors formation of **9d** (1:3.5, Table 1, entry 4). Notably, in all cases peptide **7** is a far more active catalyst than the achiral catalysts, leading to isolation of C11-derivatized material. While chromatographic separations of compounds at the diester stages are difficult and can limit yields of isolated **9**, in all cases methanolysis of the C2′-OH-derived esters leads to C11-monoesters with excellent purity.

These findings illustrate the potential of chiral catalyst-dependent, site-selective modification of polyol natural products. In addition, the discovery of catalyst-dependent modifications that reorganize natural product architecture may be of additional utility in the science of natural product analog generation. The mechanistic basis of these transformations is a frontier area of chiral catalysis, and studies of catalyst interactions with polyfunctional substrates are underway.[15]

Table 1: Site-selective reactions of erythromycin A with achiral catalyst versus **7**.



Entry		Achiral cat.[a] **8**:**9**[b]	Cat. **7**[c] **8**:**9** (yield of **9**)
1 **8a**, **9a**: R = $(CH_2)_6CH_3$		> 10:1[b]	1:9 (58%)
2 **8b**, **9b**: R = $(CH_2)_2NHBoc$		5:1[b]	1: > 10 (53%)
3 **8c**, **9c**: R = $(CH_2)_2CH{=}CH_2$		2:1[b]	1:5 (56%)
4 **8d**, **9d**: R = Et		2:1[b]	1:3.5 (28%)

[a] Reaction catalyzed by pyridine as solvent. Reactions catalyzed by NMI provide similar ratios. [b] Reactions with pyridine or NMI are generally sluggish and not preparatively useful. Consistent with the reports of Abbott Laboratories,[9] the yields of **8** (R = Me) under conditions promoted by pyridine is about 70% after 3 days reaction time. Yields of **9** under catalysis by pyridine are extremely low and difficult to quantify. Thus, peptide **7** provides unique access to **9**. [c] Yields are determined from isolated material after chromatography. In cases where co-elution with minor components occurs, conversion into the corresponding C11-monoester following methanolysis of the C2′-OH-ester delivers pure compounds for full characterization. See Supporting Information for details.

Experimental Section

General procedure for the acylation of erythromycin A: Erythromycin A (**3**, 100 mg, 0.136 mmol) was dissolved in $CHCl_3$ (100 mM, 1.36 mL) in a flame-dried vial. Triethylamine (5 equiv, 93.0 μL, 0.681 mmol) and the catalyst (5 mol%, 20.0 mM in CH_2Cl_2, 0.340 mL, 6.81 μmol) were then added sequentially. For less reactive anhydrides, 10 mol% catalyst is employed (see Supporting Information for details.) Acetic anhydride (10 equiv, 128 μL, 1.36 mmol) was added and the reaction was allowed to stir at 25 °C. Reaction progress was monitored by ^{1}H NMR (400 MHz) by removing 100 μL aliquots followed by a methanol quench. The resulting solutions were passed through a silica gel plug eluting with a $CHCl_3$/MeOH (95/5 v/v) solvent system and concentrated under high vacuum. After an appropriate time interval, the full reaction mixture was quenched by addition of methanol and passed through a silica gel plug and concentrated to dryness. If complete cleavage of the labile 2′-acetyl was desired, the unpurified reaction mixture was redissolved in MeOH and allowed to stir for 72 h. After concentration of the reaction mixture, reaction selectivity was analyzed by ^{1}H NMR (400 MHz). Individual products were isolated by silica gel column chromatography ($CHCl_3$/MeOH/NH_4OH, 14 M; 95/5/1 v/v/v) and/or semipreparative HPLC techniques.

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