Synthetic Methods

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An Approach to the Site-Selective Deoxygenation of Hydroxy Groups Based on Catalytic Phosphoramidite Transfer**

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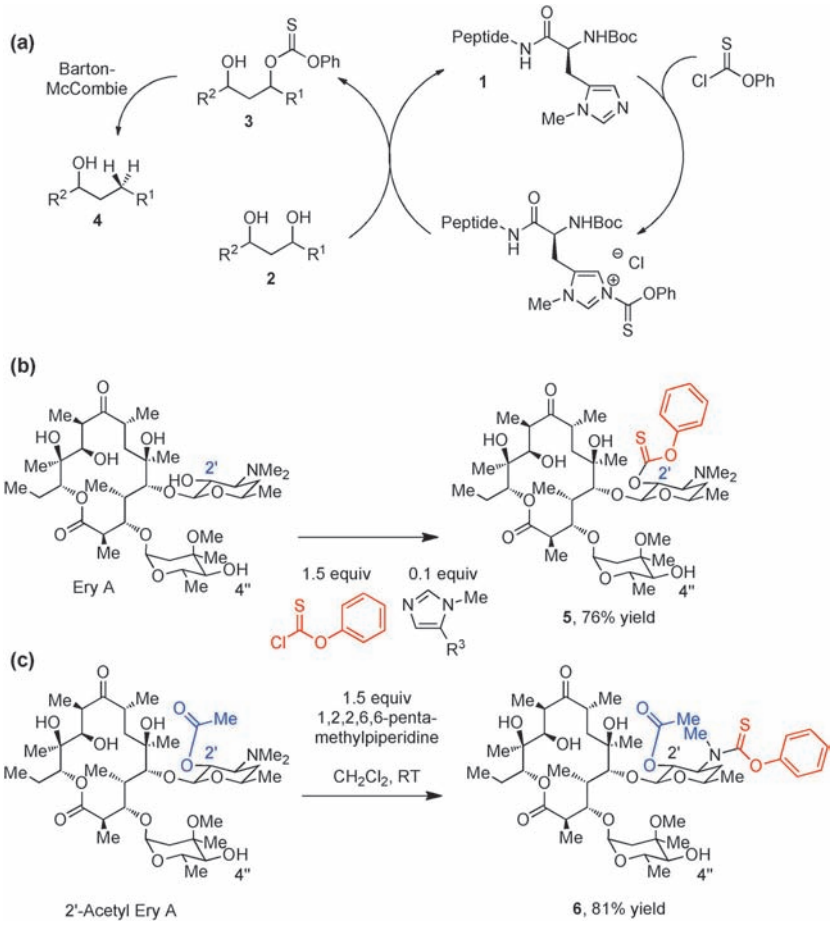
The site-selective, catalytic modification of complex molecules is a long-standing goal for chemists. Given the high efficiency of many fermentation processes, the use of natural products as scaffolds for diversification is part of many epic drug-discovery programs.[1] Yet, it is generally accepted that these research efforts are challenging, often requiring multistep syntheses of the requisite analogues,[2] re-engineered biosynthetic pathways,[3] or enzymatic modification of the natural product itself.[4] The use of chemical catalysts to alter complex scaffolds may represent a growing field with potential to impact these interdisciplinary research efforts.[5,6] The challenges at the front end of this approach include the identification of not only relevant reactions to explore, but also the inherent architectural and stereochemical molecular features that the catalyst–substrate complexes ultimately embody.

Among the more comprehensively studied scaffold-modifying processes in nature are oxidation reactions.[7] Chemists can parallel nature's course, which tends to increase the overall oxidation state of a substrate during the course of a biosynthesis.[8,9] But, how might chemists turn the biosynthetic clock back? Can chemists take nature's oxidized scaffolds and catalytically and selectively achieve deoxygenated analogues directly, without de novo synthesis of a deoxygenated, complex molecule? While enzymes that deoxygenate polyols are known,[10] they are perhaps less prevalent than their oxidase counterparts. Recognizing the power of chemical deoxygenation, chemists have developed a lexicon of deoxygenation protocols.[11] However, it might reflect the state of the art that very few deoxygenation protocols involve catalysis, and even fewer address selectivity in polyfunctional molecules. One approach to these issues is described below.



Scheme 1. a) Peptide-catalyzed site-selective thiocarbonylation as a precursor to radical deoxygenation. b) Thiocarbonylation of erythromycin A with *N*-methylimidazole catalyst. c) Thiocarbamate formation on 2′-acetylerythromycin A. Boc = *tert*-butoxycarbonyl.

Our laboratory has been exploring methods for the site-selective manipulation of polyols.[12] Among the reactions we have explored, site-selective deoxygenation is one of the more challenging.[13] We reported that peptides containing modified histidine (**1**) could indeed effect catalytic, site-selective thiocarbonylation of several simple polyols as a prelude to deoxygenation (**2**→**3**→**4**; Scheme 1 a).[14] However, a number of limitations exist. For example, when the approach is applied to erythromycin A (Ery A), side reactions can reduce efficiency. Whereas direct thiocarbonylation of Ery A under our previously developed conditions can deliver thiocarbon-

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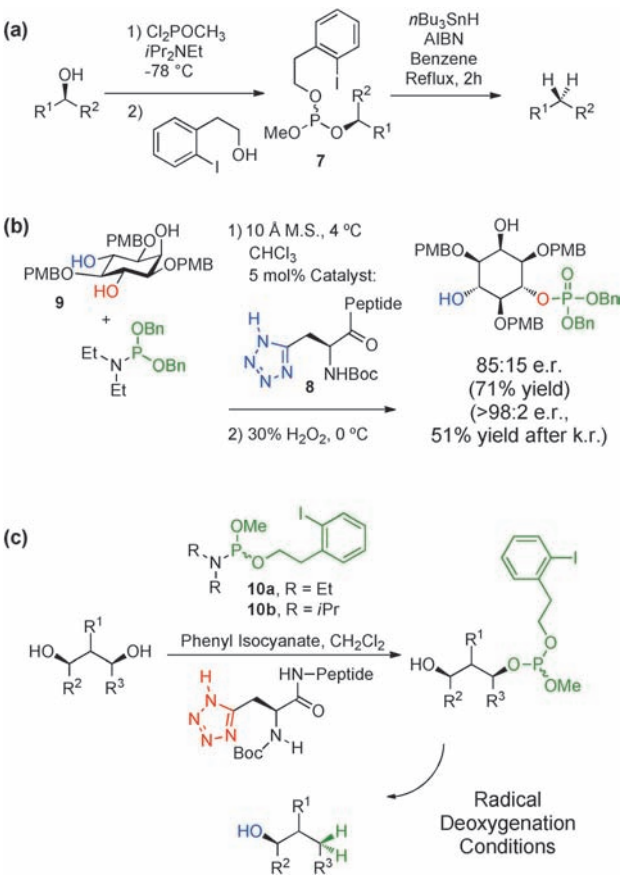
ate **5** in 76% yield (Scheme 1b), the same conditions applied to 2′-acetyl-Ery A results in dealkylation of the amino group (**6**, Scheme 1c).[15] Because natural products decorated with amino sugars are common,[16] we suspected that such side reactions would be a consistent liability with carbonyl-based electrophiles when applied to this class of structures.

To address limitations such as these, we undertook the exploration of a new catalytic cycle for site-selective deoxygenation of polyols. With the goal of achieving the mildest of conditions, such that diverse, complex natural-product functionality could be tolerated, we were drawn to the efficient deoxygenation of hydroxy groups pioneered by Koreeda and Zhang.[17] With this synthetic method, hydroxy groups are converted to the corresponding phosphites through phosphitylation with P^{III}-based chlorophosphites that contain a pendant iodoarene (**7**, Scheme 2a). Then, radical deoxygenation occurs under standard conditions. While powerful, this P^{III}-based approach is not readily adaptable to catalysis, given the high reactivity of chlorophosphites. Thus, we wondered if it might be adapted to a catalytic phosphoramidite transfer process we had recently reported.[18] In this work (Scheme 2b), we showed that the venerable phosphoramidite method described by Caruthers[19] could indeed be performed



Scheme 2. a) Dichlorophosphite strategy to form phosphite-based deoxygenation precursors. b) Peptide-catalyzed, enantio- and regioselective phosphitylation employing phosphoramidites. c) Peptide-catalyzed site-selective formation of phosphite-based deoxygenation precursors employing phosphoramidites. AIBN = azobisisobutyronitrile, PMB = *p*-methoxybenzyl, M.S. = molecular sieves, e.r. = enantiomeric ratio, k.r. = kinetic resolution.

with peptide-embedded tetrazoles as catalysts (e.g., **8**; ca. 5 mol% of the catalyst is typical for high conversion). Moreover, we showed that the approach was amenable to the transfer of stereochemical information, with desymmetrization of inositol derivative **9** as an example. The question thus became whether or not these approaches could be merged to enable catalytic, site-selective phosphoramidite transfer. The key advance required the development of previously unknown phosphoramidite **10b** (Scheme 2c), and the demonstration that it is amenable to selective transfer and subsequent deoxygenation.

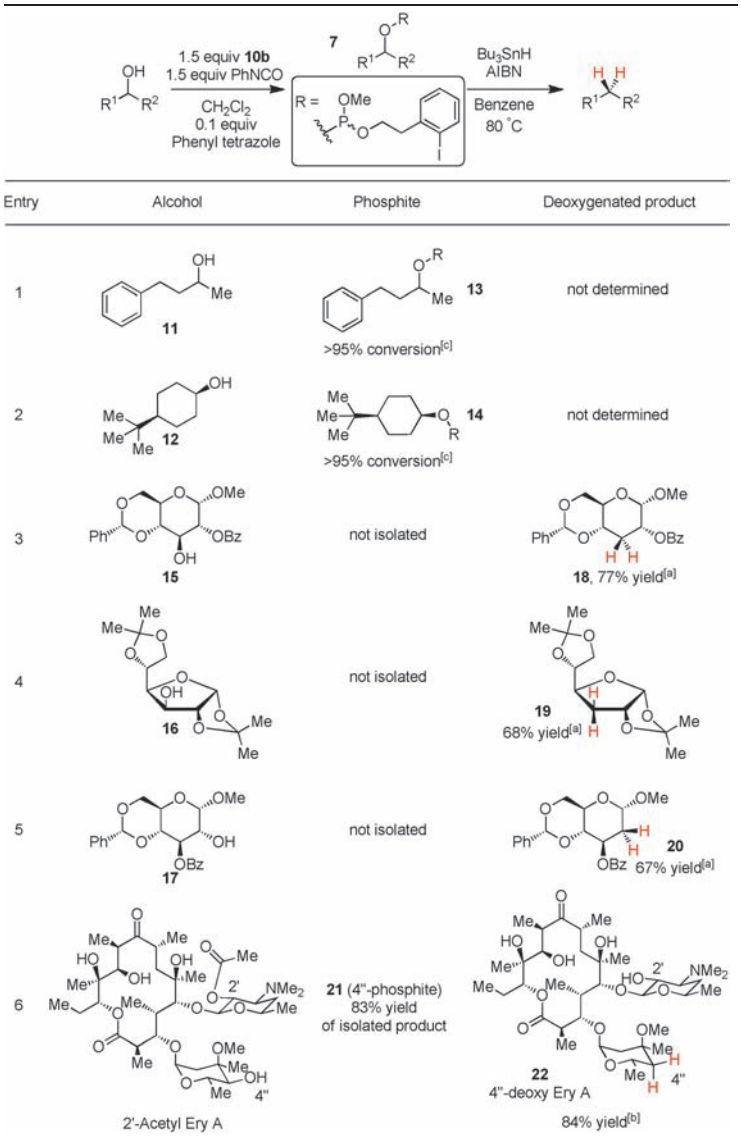
Initially, we attempted to adapt the same catalytic strategy described in Scheme 2b employing the diethylamino variant of the phosphoramidite (**10a**) and 10 Å molecular sieves.[20] These conditions, however, proved to be incompatible with low-molecular-weight substrate **11** (Table 1), and sluggish for the phosphitylation of 2′-acetyl-Ery A. Furthermore, phosphoramidite **10a**, in the absence of molecular sieves, was highly prone to hydrolysis, and decomposed in the presence of an alternative amine scavenger, phenyl isocyanate.[21]

Therefore, we pursued the synthesis of the much more stable phosphoramidite **10b**, based on diisopropylamino substitution, for use in combination with phenyl isocyanate as an amine scavenger (Scheme 2c). On a multigram scale, phosphoramidite **10b** can be synthesized from 2-(2-iodophenyl)ethanol and methyl tetraisopropyl phosphordiamidite in greater than 90% yield.[22] Not only did **10b** prove to be compatible with tetrazole catalysis (Table 1), it was also stable to both hydrolysis and oxidation over the course of several months without any special precautions.

We initially examined the catalytic phosphitylation of simple alcohols **11** and **12** in the presence of only 10 mol% phenyltetrazole as catalyst, and 1.5 equivalents each of **10b** and phenyl isocyanate (Table 1, entries 1 and 2). Both substrates **11** and **12** were completely consumed within four hours, and ^{1}H NMR spectra of the resulting crude material indicated a very clean transformation with no remaining starting alcohol and evidence for the formation of the corresponding phosphites (**13** and **14**, respectively), typically to greater than 95% conversion (^{1}H NMR spectroscopy analysis).[22] Although it was clear that the catalytic phosphitylation reaction proceeded with great efficiency, isolation of the corresponding phosphites by silica-gel chromatography proved to be much more problematic because of the persistent co-elution with the side product urea derived from reaction of the liberated diisopropylamine with the isocyanate amine scavenger. Purification was further hampered by the overall instability of the phosphite products.

Having demonstrated the feasibility of the catalytic phosphitylation reaction with simple substrates, we next sought to assess the overall deoxygenation strategy by investigating whether the crude phosphite products of more relevant, highly oxygenated substrates (Table 1, **15**, **16**, **17**; entries 3–5) could be carried through the deoxygenation step without isolation and purification of the intermediate phosphites. Such a strategy would potentially streamline the process and minimize the loss of material. Moreover, in the context of chiral natural products, the structure of the deoxygenated products would be easier to assign than the

Table 1: Catalytic phosphitylation and deoxygenation of alcohol substrates.



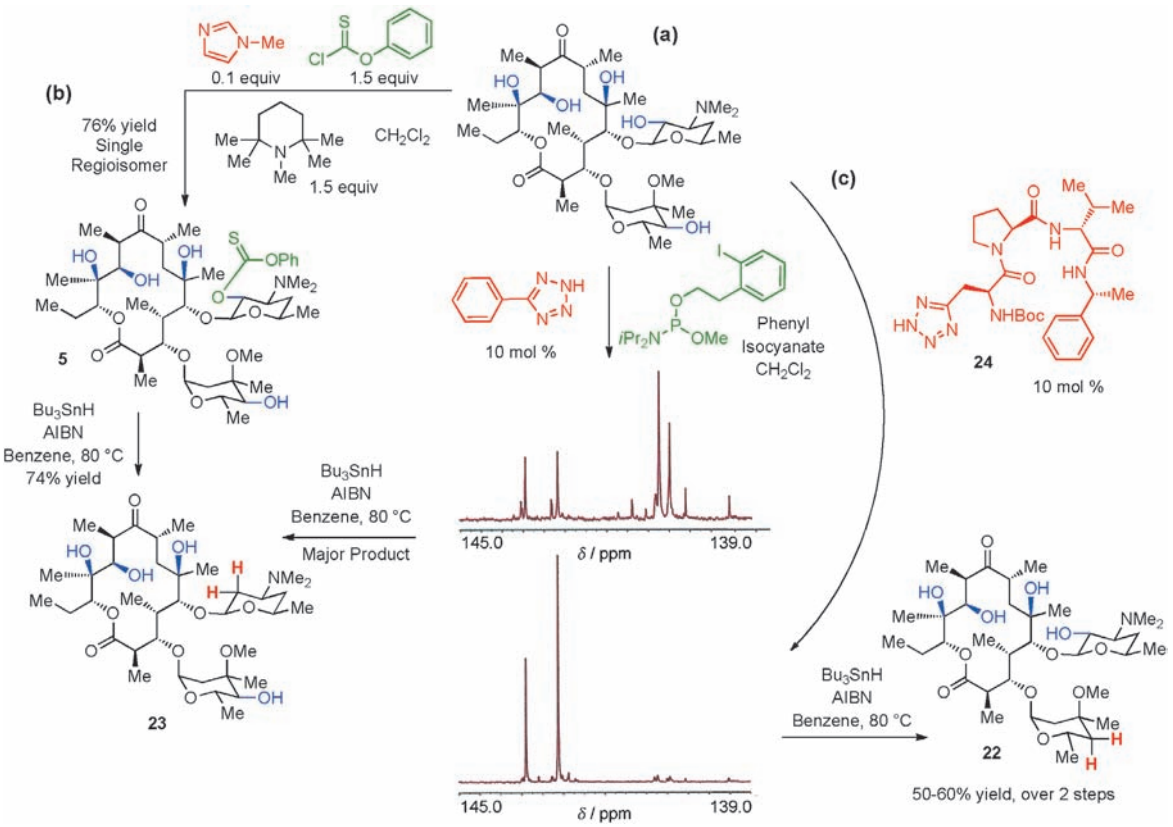
[a] Yields of the isolated deoxygenated species are given for the two-step process. [b] Yield of isolated product determined from phosphite **21** after methanol cleavage of 2′-acetyl protecting group. [c] Conversion determined by NMR spectroscopy.

epimeric P-chiral phosphites. We therefore subjected compounds **15**–**17** to the same catalytic phosphitylation conditions described for **11** and **12**. Then, after basic workup, each phosphite was immediately treated with the standard radical deoxygenation conditions. We were delighted to find that the two-step strategy gave the corresponding deoxygenated products **18**, **19**, and **20**, respectively, in good overall yields. Moreover, as shown in Table 1 (entry 6), we applied the new catalytic phosphitylation strategy to 2′-acetyl-Ery A, observing clean conversion to the 4″-phosphite product **21**, which was isolated in 83 % yield. This phosphite product was readily deoxygenated under standard conditions, and after methanolic deacylation gave 4″-deoxy-Ery A (**22**) in 84 % yield.[23]

We next wished to assess prospects for catalyst-dependent, site-selective phosphitylation/deoxygenation of a complex, native polyol with the newly developed protocol. Our hypothesis was that a peptide-based appendage to the catalytically active tetrazole moiety would provide a handle for tuning site-selectivity, in analogy to our early observations with other group transfer processes.[24] The goal was to examine whether catalyst control might overcome the well-known high reactivity of the 2′-hydroxy group of Ery A.[25] It is well precedented that the 2′-hydroxy group reacts rapidly with many carbonyl-based electrophiles, presumably through a neighboring base-assisted mechanism. As such, methods to modify the other hydroxy groups of erythromycin A generally require protection of this position. To test this prospect for catalyst-dependent reversal of site-selectivity, without recourse to the use of a protective acetyl group, we subjected Ery A to the phosphitylation conditions described above. Upon workup, we analyzed the product distribution by ^{31}P NMR spectroscopy. As indicated in Scheme 3 a, the simple catalyst phenyltetrazole gave a distribution of phosphite products, with four intense chemical shifts. By analogy to the previously isolated 2′-acetyl-4″-phosphite of Ery A (see Table 1, entry 6, **21**), we believe that the two ^{31}P chemical shifts at $\delta =$ 143 and 144 ppm correspond to the two ^{31}P-epimers of the 4″-regioisomer. The other most significant product of the reaction, with ^{31}P-chemical shifts at $\delta = 140.0$ and 140.5 ppm, would appear to be the alternative 2′-phosphite. Subjection of this mixture to deoxygenation conditions gives a corresponding mixture of deoxygenation products. Of the two major products that are formed, one is indeed identical to **23** that was obtained from the deoxygenation of thiocarbonyl **5** (Scheme 1 b). The other may be assigned as the 4″-regioisomer (**22**), albeit at low relative abundance. Notably, this catalytic protocol delivers the mixture in an approximate 3:1 ratio (^{1}H NMR spectroscopy analysis), reflecting an inherent preference for the 2′-deoxy isomer (**23**), with the simple phenyltetrazole catalyst.[22]

On the other hand, the peptide-embedded tetrazole-based catalyst **24** provides the putative 4″-regioisomer with near-complete selectivity (Scheme 3 c). Furthermore direct radical deoxygenation of the corresponding crude reaction mixture gives 4″-deoxy-Ery A (**22**), in 50–60 % yield of isolated product, from Ery A.

It is notable that the peptide-catalyzed phosphitylation/deoxygenation protocol results in both clean reactions and altered selectivity in comparison to the results achieved with the simple phenyltetrazole catalyst. Moreover, it is also relevant to our efforts that the most efficient paths to either the 2′-deoxy-Ery A (**23**) or the 4″-deoxy-Ery A (**22**) turn out to employ different protocols—thiocarbonylation with a simple catalyst in the former case, and phosphitylation with a peptide-embedded tetrazole in the latter case. These findings emphasize the need to evaluate multiple approaches in parallel for the goal of site-selective deoxygenation of complex polyols, in pursuit of multiple and various deoxygenated analogues.



Scheme 3. a) Nonselective, phenyltetrazole-catalyzed phosphitylation gives multiple phosphite products as shown in the ^{31}P NMR spectrum (crude sample). Deoxygenation yields **23** as the major product. b) *N*-methylimidazole-catalyzed thiocarbonylation and subsequent radical deoxygenation to give **23**. c) Peptide **24** directly delivers the 4″-phosphite product (^{31}P NMR spectrum, crude sample) for efficient deoxygenation to give 4″-deoxyerythromycin A (**22**). A larger-scale representation of the NMR spectra is presented in the Supporting Information as Supplemental Figure 3.

We conclude this report with several thoughts regarding these findings. First, we are intrigued by our ongoing observation of catalyst-dependent reversal of inherent selectivity in derivatization reactions of this type.[5] From the pragmatic perspective, it may be that this approach will represent an addition to the tools available to chemists for the direct manipulation of complex structures. Notably, our work in this area has revealed that there is a premium on the use of catalysts for complex molecule derivatizations since improvements in selectivity can greatly facilitate isolation of pure materials and, eventually, their large-scale synthesis. Maybe most important, however, is the identification of orthogonal catalysts and protocols that provide access to unique natural product analogues. Perhaps we can aspire to comprehensive and general approaches to problems like catalytic, site-selective deoxygenation of complex structures. But, our studies in this area reveal that, at present, diverse approaches may be most enabling. In this vein, we also anticipate that libraries of catalysts, for example those bearing the tetrazolylalanine, will be needed to generalize these findings to other classes of compounds. Our extension of these studies to other families of complex-molecule deoxygenations are ongoing and shall be reported in the future.

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