Substitution Reactions

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Isoxazole-Assisted Direct Substitution of the Hydroxy Group in α-Ketols: Introduction of Angular Substituents in a Polycyclic System**

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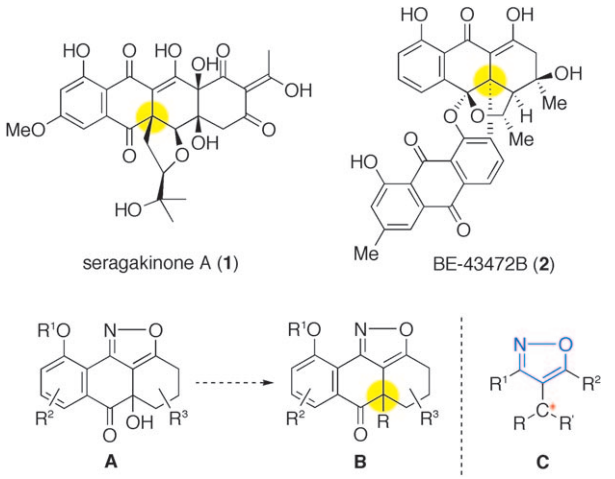
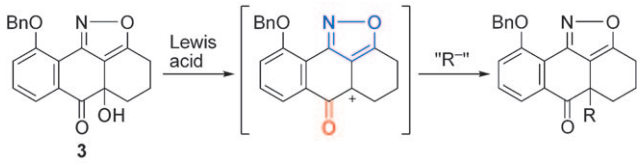
The type-II polyketide biosynthetic pathway produces a vast array of polycyclic natural products such as **1**[1] and **2**,[2] attracting the attention of the biochemical and synthetic communities.[3] In our continued synthetic endeavors towards these compounds, we searched for viable methods for introducing the characteristic angular substituents (Scheme 1).[4] We envisaged α-ketol **A**[5] as a key platform to achieve this goal, hoping that the isoxazole moiety would serve not only as a 1,3-dicarbonyl equivalent,[6] but also as a



Scheme 1. Approach to polyketide-derived polycyclic natural products with angular substituents.

"guiding functionality" to install an angular substituent (**A** → **B**). This installation can hopefully be facilitated by the recently discovered ability of isoxazoles to stabilize the α-cationic species **C**.[7]

By recognizing these aspects, we reasoned that ketol **3** would be amenable to the direct S_N1-type substitution of the hydroxy group (Scheme 2).[8] Although formation of a cation next to a carbonyl group is disfavored,[9] we hoped that the isoxazole unit would override the deficit. If viable, the process would become a straightforward approach to angularly substituted polycyclic natural products, such as **1** and **2**.



Scheme 2. Direct installation of an angular substituent. Bn = benzyl.

Herein, we report the affirmative answer to this challenge, that is, the isoxazole-assisted, direct substitution of α-ketol **3** with various nucleophiles to therefore allow the installation of angular substituents in polycyclic systems.

The initial feasibility study is illustrative [Eq. (1)]: Upon treatment of enantiomerically enriched α-ketol (*R*)-**3** (98% *ee*)[5] with allyltrimethylsilane (3.0 equiv) in the presence of $BF_3{\cdot}OEt_2$ (1.0 equiv, CH_2Cl_2, RT, 0.5 h), the desired reaction proceeded smoothly to give the α-allyl ketone **4a** in 94% yield. Notably, **4a** was completely racemic, thus suggesting the intermediacy of a well-developed cationic species next to the isoxazole.

(1)

Encouraged by the promising opportunities for installing various angular substituents by the S_N1 pathway, we examined the scope of this reaction, which led us to confirm its broad applicability (Table 1). Heteronucleophiles, such as alcohol **5** and thiol **6**, smoothly reacted at 0 °C to give ether **4b** and sulfide **4c** in excellent yields (Table 1, entries 1 and 2). Furthermore, installation of angular aryl or (hetero)aryl groups by the Friedel–Crafts pathway proved to be achievable (Table 1, entries 3–9). Phloroglucinol derivative **7** cleanly gave ketone **4d** in 92% yield (Table 1, entry 3), and *N*-methylindole (**8**) reacted at ambient temperature, to give exclusively the 3-substituted product **4e** in 95% yield (Table 1, entry 4). While phenol (**9**) gave a regioisomeric

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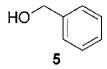
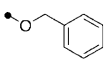
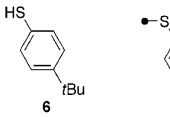
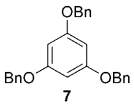
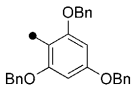
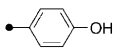
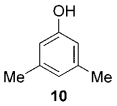
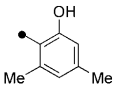
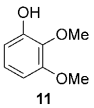
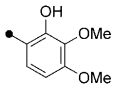
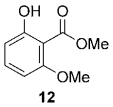
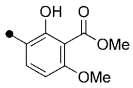
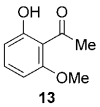
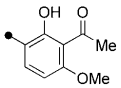
Table 1: Reaction of α-ketol **3** with various nucleophiles.[a]

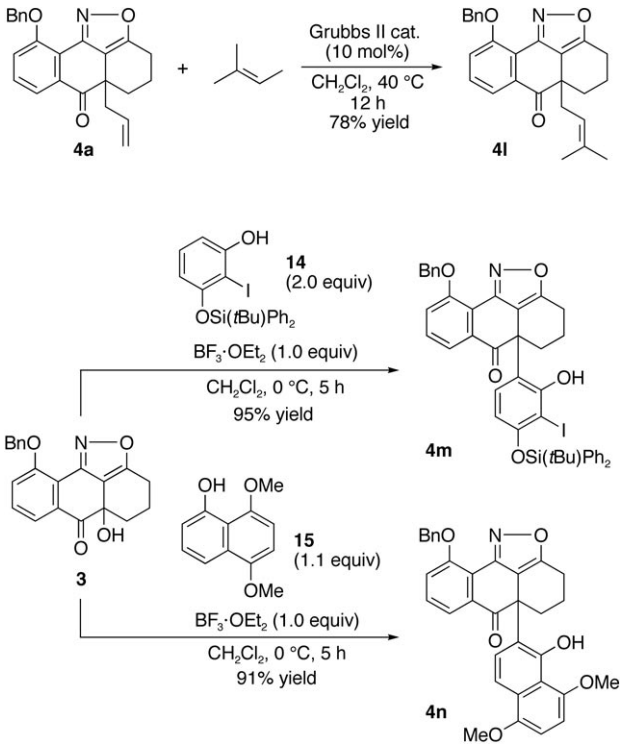
Entry	Nucleophile	R[b]	*T* [°C]	*t* [h]	Yield [%]
1[c]	 **5**		0	10	87 (**4b**)
2	 **6**		0	6	93 (**4c**)
3	 **7**		0	9	92 (**4d**)
4	 **8**		RT	8.5	95 (**4e**)
5	 **9**		0→RT	1	36[d] (**4f**)
					48[d] (**4g**)
6[e]	 **10**		0	4	93 (**4h**)
7[e]	 **11**		0	8	90 (**4i**)
8[e]	 **12**		RT	1.5	90 (**4j**)
9[e]	 **13**		RT	16.5	94 (**4k**)

[a] Unless otherwise indicated, $BF_3{\cdot}OEt_2$ (1.0 equiv) and nucleophile (3.0 equiv) in CH_2Cl_2 (0.1 M) at the temperature indicated. [b] Dots represent the position of the connectivity. [c] $BF_3{\cdot}OEt_2$ (1.5 equiv). [d] Crude products were acetylated prior to the analysis. [e] Nucleophile (2.0 equiv).

mixture of *ortho*- and *para*-products, **4f** and **4g** (Table 1, entry 5), substituted phenols **10**–**13** selectively reacted at the *ortho* position to give **4h**–**4k** (Table 1, entries 6–9). Electron-rich phenols, **10** and **11**, reacted smoothly at 0°C (Table 1, entries 6 and 7). Although the phenols **12** and **13** with electron-withdrawing groups were less reactive, the reactions smoothly proceeded at room temperature to afford the corresponding products **4j** and **4k** in excellent yields.

At this stage, we embarked on the advanced model studies, en route to isoprenoid hybrid **1** and bis(anthraquinone) **2** (Scheme 3). Associated with the regioselective installation of an angular prenyl group, we examined an indirect approach through cross metathesis:[10] The angular allyl group in **4a** was converted into a prenyl group to give **4l** in 78% yield by treatment with an excess amount of 2-methyl-2-butene in the presence of the second-generation Grubbs catalyst.

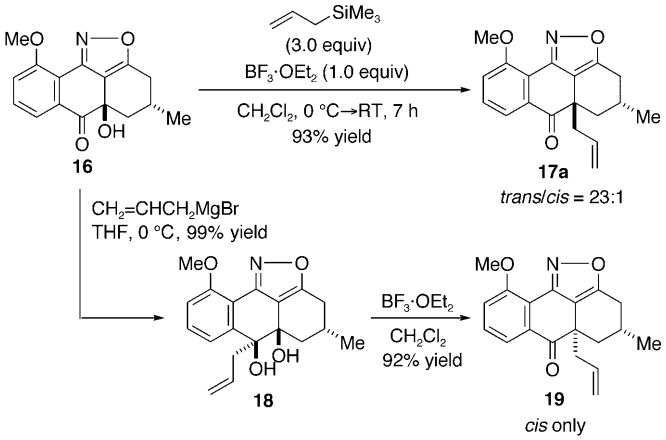
As a model for the stereoselective installation of an angular anthraquinone unit, which is characteristic to **2**,[11] we examined the reactions of iodophenol **14**[12] and naphthol



Scheme 3. Model studies toward **1** and **2**.

15.[13] Gratifyingly, both substitution reactions smoothly proceeded in an *ortho*-selective manner to afford the corresponding products **4m** and **4n** in high yields.

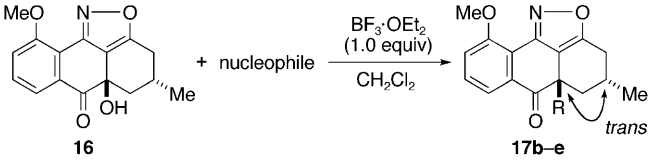
Scheme 4 is an example for the diastereoselective version of the process, in which α-ketol **16**, having a methyl group at the β position to the reacting center, was used as the model substrate.[14] Notably, the stereochemical complementarity to the pinacol-based approach was observed in the case of the allylation to ketol **16**. Upon treatment with allylsilane and $BF_3{\cdot}OEt_2$, ketol **16** underwent a retentive allylation from the opposite side to the methyl group, to afford ketone **17a** in high yield. By contrast, the inverted installation of an angular allyl group to α-ketol **16** by the pinacol-based approach gave access to the isomeric ketone **19** as the sole product through the nucleophilic addition and the 1,2-shift.

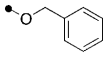
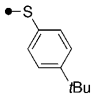
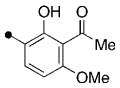
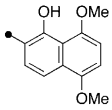


Scheme 4. Complementary approaches for an angular allylation.

The diastereoselectivity was also observed with other nucleophiles (Table 2). Heteronucleophiles exclusively gave the corresponding *trans* products **17b** and **17c** in high yields (Table 2, entries 1 and 2). The reactions of phenol **13** and naphthol **15** occurred regio- and stereoselectively to afford **17d** and **17e** in excellent yields (Table 2, entries 3 and 4).

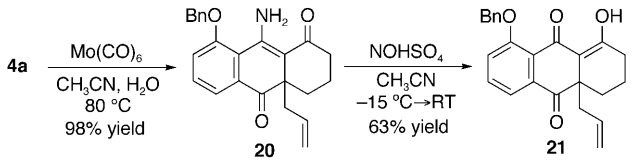
Table 2: Reaction of α-ketol **16**.[a]



Entry	R	*T* [°C]	*t* [h]	Yield [%] (*trans*/*cis*)[b]
1[c]		0→RT	3	80 (**17b**) (>99:<1)
2		0→RT	3.5	82 (**17c**) (>99:<1)
3		RT	18	81 (**17d**) (15:1)
4		0→RT	2	93 (**17e**) (>99:<1)

[a] Unless otherwise indicated, $BF_3{\cdot}OEt_2$ (1.0 equiv) and nucleophile (1.1 equiv) in CH_2Cl_2 (0.1 M) at the temperature indicated. [b] The stereochemical outcomes were determined by X-ray analysis (see the Supporting Information). [c] $BF_3{\cdot}OEt_2$ (3.0 equiv).

Scheme 5 illustrates the unmasking of β-diketone **21** through the reductive conversion of ketone **4a**.[15] The reductive opening of the isoxazole ring in **4a** with molybdenum hexacarbonyl[16] gave vinylogous amide **20**, which turned out to be unexpectedly resistant at undergoing hydrolysis by usual acid hydrolysis.[17] However, we were pleased to find that the desired hydrolysis could be executed with nitrosylsulfuric acid[18] to give β-diketone **21** in 63% yield.



Scheme 5. Conversion of isoxazole **4a** into 1,3-diketone **21**.

In conclusion, the isoxazole-assisted S_N1 substitution of α-ketol allows facile introduction of angular substituents to polycyclic structures. The efficient ability of the isoxazole unit to stabilize the α-cation has promising potential in organic synthesis, and further studies are underway in our laboratories.

Experimental Section

Typical procedure for the S_N1 substitution of α-ketol **3** with allyltrimethylsilane: $BF_3{\cdot}OEt_2$ (20 μL, 0.16 mmol) was added to a solution of α-ketol **3** (53 mg, 0.15 mmol) and allyltrimethylsilane (52 mg, 0.46 mmol) in CH_2Cl_2 (1.5 mL) at 0°C. The reaction mixture was allowed to warm to room temperature. After stirring for 0.5 h, it was cooled to 0°C and saturated $NaHCO_3$ was added. The products were extracted with EtOAc (×3) and the combined organic extracts were washed with brine, dried over Na_2SO_4, and concentrated under reduced pressure. The residue was purified by PTLC with *n*-hexane/EtOAc (2:1) to give ketone **4a** (53 mg, 94%) as a white solid.

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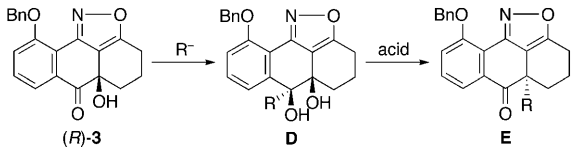

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[15] For the oxidative conversion of isoxazoles into α-hydroxy-β-diketones, see: H. Takikawa, A. Takada, K. Hikita, K. Suzuki, *Angew. Chem.* **2008**, *120*, 7556 – 7559; *Angew. Chem. Int. Ed.* **2008**, *47*, 7446 – 7449.

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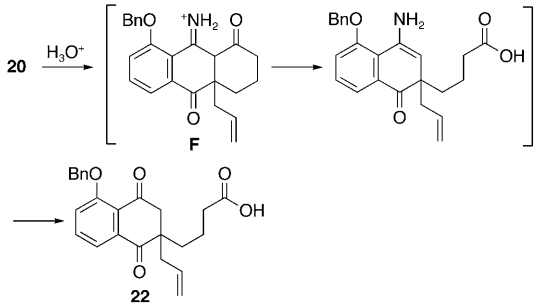
[17] Upon exposure to H_2SO_4 (3 M in THF, 40 °C, 6 h), vinylogous amide **20** underwent slow decomposition to give acid **22** (78 %) presumably by a retro-Claisen reaction of intermediary iminium **F** as shown in the scheme below. We confirmed that β-diketone **21** was most resistant to decomposition under the same reaction conditions (3 M H_2SO_4 in THF, 40 °C), further supporting our mechanistic postulate.



[18] For hydrolysis of amides with nitrosonium salts, see: G. A. Olah, J. A. Olah, *J. Org. Chem.* **1965**, *30*, 2386 – 2387.