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Enol triflates derived from the Wieland–Miescher ketone and an analog bearing an angular acetoxymethyl group: their highly regioselective synthesis and Stille coupling with vinyl(tributyl)tin

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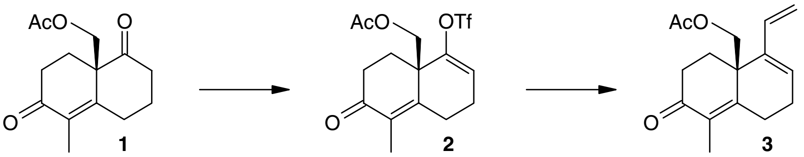
Abstract—A highly selective synthesis of the enol triflate derived from the 9-keto group was achieved directly from the Wieland–Miescher ketone or an analog in kinetic conditions with LHMDS/THF–HMPA and Comins reagent. The other isomeric triflates were also obtained selectively in other conditions and their specific Stille coupling with vinyl(tributyl)tin was achieved in high yields. The structures of the different isomers were determined unambiguously by IR, UV, ^{1}H and ^{13}C NMR (COSY, HMBC, HSQC, and NOE). The results previously reported by Pal for the Wieland–Miescher ketone have therefore to be corrected, due to erroneous structural assignments.

1. Planned sequence (Scheme 1)

As described in the accompanying communication,[1] our synthetic approach to enfumafungin started with the chiral Wieland–Miescher ketone analog **1** (ee 85%). The transformation of **1** into diene **3** was required for further planned Diels–Alder reaction, and involved the 9-enol triflate **2** and its Stille coupling with vinyl(tributyl)tin (Scheme 1). An analogous sequence had previously been reported by Pal for the Wieland–Miescher ketone, to afford specifically in high yield the desired triflate (70%) and the corresponding diene (95%).[2] This route was claimed to be superior to previous methodologies which appear to be quite versatile with respect to the diene isomerization.[3]

2. Products obtained in the conditions described by Pal (Scheme 2)

We first used the conditions described by Pal which, starting from **1**, afforded after chromatography in high yields a unique triflate (93%) and the corresponding Stille coupling product (85%), and no traces of other isomers were observed. However, IR and UV clearly showed that they did not have the desired structures **2** and **3**, but were regioisomers instead, since these data indicated no conjugated ketone. Further 2D NMR data (^{1}H and ^{13}C) and significantly observed NOE clearly showed that their structures were, respectively, **4** for the triflate and **5** for the coupling product (Scheme 2).[4] Hence, we reexamined the Wieland–Miescher ketone **6**



Scheme 1.

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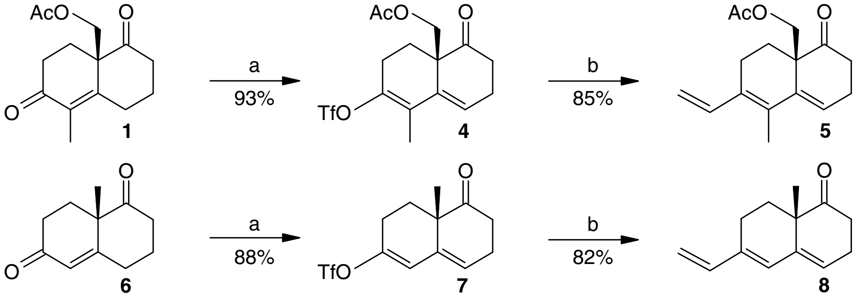


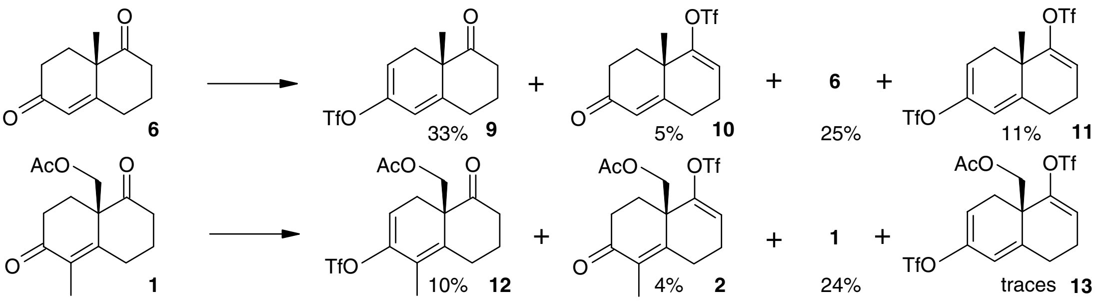
Scheme 2. Reagents and conditions: (a) 2,6-di-*t*-butyl-4-methylpyridine (2.0 equiv), Tf_2O (1.9 equiv), CH_2Cl_2, 0 °C to rt, 1 h; (b) $Pd_2(dba)_3{\cdot}CHCl_3$ (2.5 mol %), $AsPh_3$ (10 mol %), NMP, vinyl(tributyl)tin (1.1 equiv), rt, 1 h.

under Pal's reaction conditions and the results were quite comparable with those obtained by us for **1**: the reactions again gave a single product, for the triflate (88%) and the corresponding coupling product (82%) with no other isomers produced. Again, UV and IR spectra clearly excluded a conjugated ketone for the isolated products and their structures were unambiguously assigned to **7** and **8**, respectively, by ^1H and ^{13}C NMR (COSY, HSQC, HMBC, and NOE) (Scheme 2).[4] Moreover, ^1H and ^{13}C NMR chemical shifts published for the enol triflate isolated by Pal matched quite well with those of the triflate we obtained, and were shown to differ significantly from those of the other regioisomers we obtained subsequently (Supplementary data), clearly showing that the same compound was obtained. However, Pal did not report any IR or UV for the triflate, and any data at all for the coupling product.[2] Again, UV and IR spectra definitely exclude a conjugated ketone for the isolated products, and their structures were unambiguously shown to correspond to **7** and **8**, respectively (Supplementary data).[4] Consequently, the results published by Pal have to be corrected, due to erroneous structural assignments.

3. Wieland–Miescher ketone and analog: kinetic enolates and derived triflates or phosphates (Schemes 3–5)

As the preceding results were obtained in thermodynamic conditions (2,6-di-*t*-butyl-4-methylpyridine, Tf_2O), we decided to examine kinetic conditions in order to try to get the desired structures **2** and **3**. Thus, enolate formation by inverse addition with LiHMDS in THF, at −78 °C, and subsequent addition of the enolate solution to a solution of an excess $PhNTf_2$ in THF at −78 °C and further reaction from −78 °C to rt led to quite disappointing results for the Wieland–Miescher ketone **6** and its analog **1**, since triflates **10** (5%) or **2** (4%) derived from chemoselective enolization of the 9-ketone were minor products. Those conditions led to the highly regioselective enolization of the conjugated ketone at the 2-position, thus affording triflates **9** (33%) or **12** (10%). The previously obtained triflates **4** or **7** were not observed here. The reaction of **6** also afforded bis-triflate **11** which was isolated (11%), and starting material was still recovered in each case after the chromatography, **6** (25%) or **1** (24%). Moreover, diketone **1** led significantly to more degradation than **6**, in the same conditions (Scheme 3). The structures of triflates **9** and **12**, **10** and **2** were unambiguously demonstrated by IR and UV (isolated ketone or conjugated ketone, respectively), and that of the bis-triflate **11**, by their ^1H and ^{13}C NMR (COSY, HSQC, and HMBC).[4]

At this point, we had some doubts about the real 'quench' of the kinetic enolates in those reactions, since $PhNTf_2$ is known to be quite sluggish as an electrophile,[5] reacting most usually with enolates only by warming up to ca. −30 to 0 °C. However, some examples are found for this reagent for quenching a kinetic enolate derived from a single ketone.[6] In order to check the quench conditions, we envisaged a more reactive electrophile such as $ClP(O)(OEt)_2$. By a search of such reactions, we became aware of a previous



Scheme 3. Reagents and conditions: addition of **1** or **6** in THF to LHMDS (1.54 equiv), THF, −78 °C, 1 h, then enolates solution addition by transfer under argon, to a solution of $PhNTf_2$ (1.54 equiv) in THF at −78 °C, and then, −78 °C to rt, in 1 h 40 min for **1**, or 3 h 20 min for **6**.