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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

Nicolas Zorn and Robert Lett*

Unité Mixte CNRS-AVENTIS Pharma (UMR 26) 102, route de Noisy, 93235 Romainville, France

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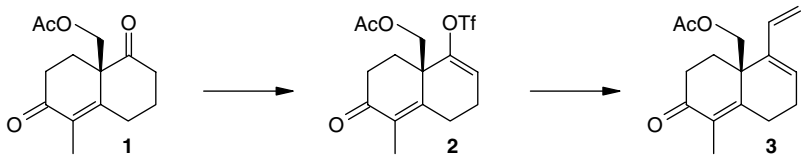
Abstract—A highly selective synthesis of the enol triflate derived from the 9-keto group was achieved directly from the Wieland–Miescher ketone or an analog in kinetic conditions with LHMDS/THF–HMPA and Comins reagent. The other isomeric triflates were also obtained selectively in other conditions and 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.

* Corresponding author at present address: ICMMO, UMR CNRS 8182, Bâtiment 410, Université de Paris-Sud, 91405 Orsay Cedex, France. Tel.: +33 1 69 15 63 03; fax: +33 1 69 15 46 79; e-mail: robert.lett@icmo.u-psud.fr

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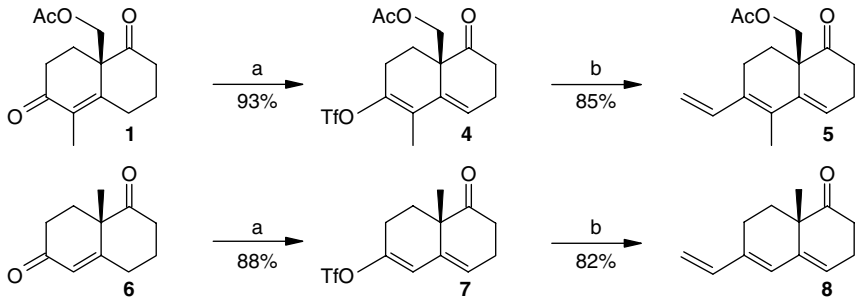


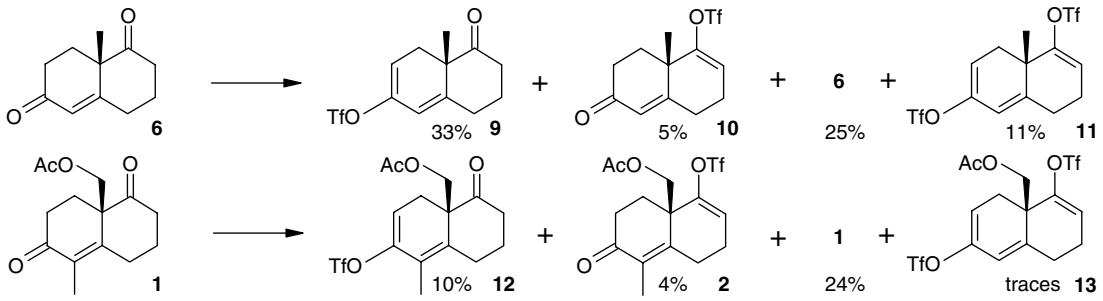
Scheme 2. Reagents and conditions: (a) 2,6-di-*t*-butyl-4-methylpyridine (2.0 equiv), Tf_2O (1.9 equiv), CH_2Cl_2, 0 °C to rt, 1 h; (b) $Pd_2(dba)_3{\cdot}CHCl_3$ (2.5 mol %), $AsPh_3$ (10 mol %), NMP, vinyl(tributyl)tin (1.1 equiv), rt, 1 h.

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

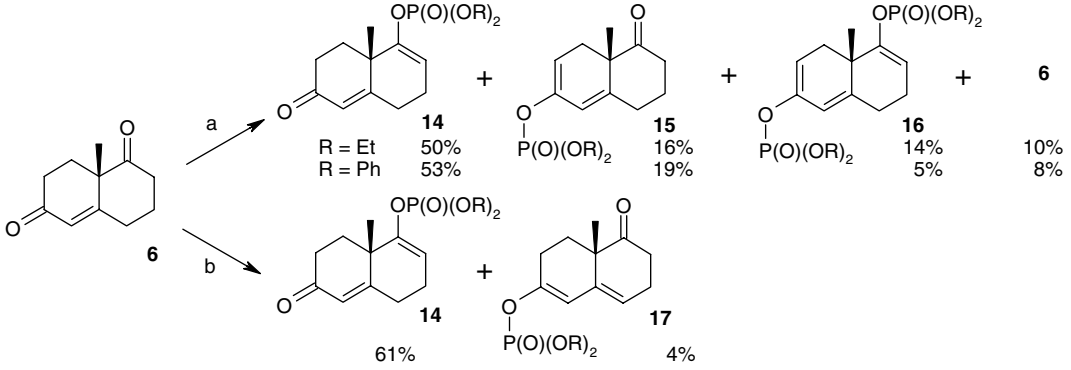


Scheme 3. Reagents and conditions: addition of **1** or **6** in THF to LHMDS (1.54 equiv), THF, −78 °C, 1 h, then enolates solution addition by transfer under argon, to a solution of $PhNTf_2$ (1.54 equiv) in THF at −78 °C, and then, −78 °C to rt, in 1 h 40 min for **1**, or 3 h 20 min for **6**.

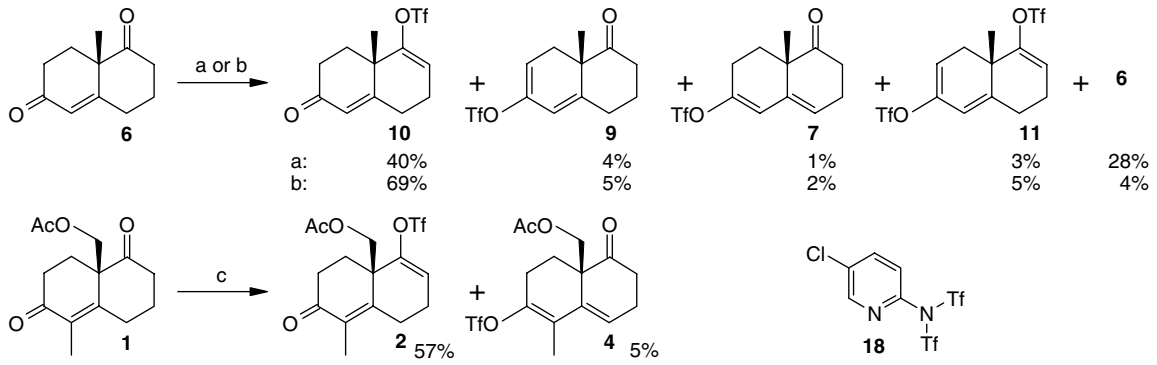
communication of Grieco who first examined the selective formation of the lithium enolate derived from the 9-ketone of the Wieland–Miescher ketone.[7] Thus, Grieco reported high yields for the reactions of the 9-lithium enolate with several electrophiles by addition of diketone **6** to LDA (1.1 equiv) in THF at −78 °C, then keeping the solution at −78 °C for 20 min to ensure complete enolate formation. Quite unusually, however, for generating a kinetic monoenolate from a diketone, the enolate solution was then allowed to warm up to 0 °C before the addition of the electrophile (MeI, Ac_2O, TMSCl, $ClP(O)(OEt)_2$). Even, more puzzling, the enolate solution was treated at −10 °C with $ClP(O)(NMe_2)_2$ in the presence of HMPA (1 equiv) to yield the 9-enol bis-dimethylaminophosphonamide.[7] In fact, there are very few such examples of highly selective kinetic monoenolate formation starting from a diketone, since equilibration is intrinsically a problem by warming-up or by dissociation of the enolate ion pair, in addition to be able to achieve quench conditions by the electrophile.[8] Thus, we first reexamined again the formation of the enol phosphates derived from the Wieland–Miescher ketone, in order to clarify the reaction conditions required to obtain the desired enolate and its quench. We examined the mode of addition either of the base (LDA, LHMDS) or of the electrophile (DEPCl, DPPCl), the stoichiometry of the reagents, temperature effects in the two steps and associated time intervals. In pure THF, we obtained the 9-enol diethyl phosphate **14** in 50–53% best reproducible isolated yields, lower than that reported by Grieco et al. (85%).[7] We also could not avoid the formation of other products (Scheme 4). The best results afforded pure **14** in 61% yield after chromatography and were obtained by the addition of a THF solution of diketone **6** and HMPA (5 equiv) to a solution of LHMDS (1.2 equiv) in THF, at −78 °C, subsequent warm-up from −78 °C to rt in 2 h 30 min, before addition of DEPCl (1.5 equiv), and further stirring of the reaction mixture at rt for 25 min (Scheme 4). We checked that inverse addition of diketone **6** to LDA (or LHMDS) (1.1 equiv) produced mostly the dienolate corresponding to **16** after DEPCl quench, this at half addition of the diketone. The further added diketone is deprotonated by the dienolate, thus giving first at low temperature the monoenolate leading to **15**, as a major species. This enolate is then involved in a kinetic interconversion which favors the monoenolate leading to **14**, when warming up to 0 °C–rt.[4] Quite significantly, in the presence of HMPA (5 equiv), we obtained the best selectivity and yield for **14**, but could not avoid a small amount of product **17** derived from the thermodynamic monoenolate. This showed that we were at the limit conditions for equilibration. Our results are in good qualitative agreement with the previous report of Grieco et al.,[7] and later results of Hagiwara et al. concerning reactions with methyl acrylate.[9] This last work clearly showed that the electrophile can shift the dynamic interconversion of the enolates derived from the Wieland–Miescher ketone, by its faster reaction with one of the enolates depending on the nature of the electrophile.

We then turned to Comins reagent **18**,[5,10] in order to use an electrophile which was more reactive than $PhNTf_2$ (Scheme 5). In preliminary experiments with the Wieland–Miescher ketone, use of the Comins reagent in the same conditions as previously with DEPCl, in anhydrous THF alone, afforded desired triflate **10** in 40% isolated yield after chromatography. Variation of the different factors gave results analogous to those observed before.[4] Finally, addition at −78 °C of the base to the THF solution of the diketone and HMPA, and same remaining procedure improved the yield of **10** to 69% isolated yield.

However, the same reaction conditions applied to **1** led mostly to degradation products which could not be characterized, probably resulting from the acetate cleavage. It is worth to point out that, for all reactions with **1**, a fresh commercial solution of LHMDS (1.0 M in THF) was always used and titrated just before use by Ireland's method[11] and for total basicity, in order to check for a very low LiOH concentration (0.02 M). LHMDS solutions which had an appreciable LiOH concentration always led to poorer results. A thorough study showed that HMPA was necessary, but that HMPA and



Scheme 4. Reagents and conditions: (a) addition of LHMDS (1.3 equiv) in THF to **6** (0.075 M) in THF, at −78 °C, then −78 °C to rt in 2 h, and rt for 30 min before addition of neat freshly redistilled DEPCl or DPPCl (2.0 equiv) at 0 °C, and then 0 °C, 20 min; (b) addition of **6** (0.15 M in THF with anhyd HMPA, 5.0 equiv) to LHMDS (1.2 equiv) in THF at −78 °C, then −78 °C to rt in 2 h 30 min, and rt for 30 min, then addition of DEPCl (1.5 equiv) and rt, 25 min.



Scheme 5. Reagents and conditions: (a) addition of LHMDS (1.15 equiv) in THF to **6** (0.15 M in THF) at −78 °C, then −78 °C to rt in 5 h 10 min, and rt for 30 min before transfer of the enolates solution to dry **18** (1.5 equiv) in THF at rt, and then rt for 1 h; (b) addition of LHMDS (1.15 equiv) in THF to **6** (0.15 M in THF) and anhydr. HMPA (5.0 equiv), at −78 °C, then −78 °C to rt in 3 h, and rt for 30 min before addition of dry **18** (0.56 M in THF, 1.5 equiv) at rt, and then rt for 1 h; (c) LHMDS (1.0 M in THF, 1.05 equiv) added to **6** (0.107 M in THF) and anhydr. HMPA (2.0 equiv), at −78 °C, then 10 min at −78 °C before addition of dry **18** (0.187 M in THF, 1.2 equiv), and subsequently −78 to −50 °C in 50 min, then transfer of the reaction mixture to cold Et_2O (−50 °C) for aq NH_4Cl quench.

LHMDS equivalents had to be adjusted, and very importantly that the reaction mixture should not warm up over −50 °C.[4]

The formation of triflate **2** could then be optimized using the following procedure: after dropwise addition of the LHMDS (1.05 equiv) solution in THF (1.0 M) to the stirred solution of diketone **1** in THF, in the presence of HMPA (2.0 equiv), at −78 °C, the enolate solution was then kept for 10 min at −78 °C; after further addition of a THF solution of Comins reagent **18** (1.2 equiv) at −78 °C, the reaction mixture was allowed to warm up to −50 °C in 50 min, and then poured immediately into cold ether (−50 °C) for subsequent quench with aq NH_4Cl and extraction. This procedure afforded the desired triflate **2** in 57% isolated yield after chromatography, and only 5% of **4**, with no more starting material and no other by-products (Scheme 5).

4. Stille couplings with vinyl(tributyl)tin (Scheme 6)

The Stille coupling of each triflate was achieved with vinyl(tributyl)tin in the same conditions as those used previously for **4** and **7** (Scheme 2), and afforded specifically the corresponding 1,3-diene in high yield, with no trace of isomerization, due to the mild conditions (Scheme 6). On the other hand, we were unable to achieve palladium-catalyzed couplings of enol phosphate **14** (R = Et or Ph), with either $AlMe_3$ or Al(vinyl)$_3$, in contrast with the cyclohexanone derived enol phosphate coupling reported by Nozaki and co-workers,[12] or with vinyl(tributyl)tin. We showed that in fact no oxidative addition occurred on **14**, whatever the phosphine (PPh_3, PCy_3, P-*t*-Bu_3), probably due to steric hindrance. These observations are in strong contrast with the easy couplings of the triflates reported herein where no significant steric effect is observed.[4]

As a conclusion, we showed that the structures assigned previously by Pal[2] have to be corrected, and that the Stille coupling is a very efficient method for the synthesis of the conjugated dienes reported herein. The isomeric enol triflates derived from the Wieland–Miescher ketone **6** or analog **1** are reported here for the first time and should also be useful for other Stille or Suzuki couplings in natural products synthesis.

Acknowledgements

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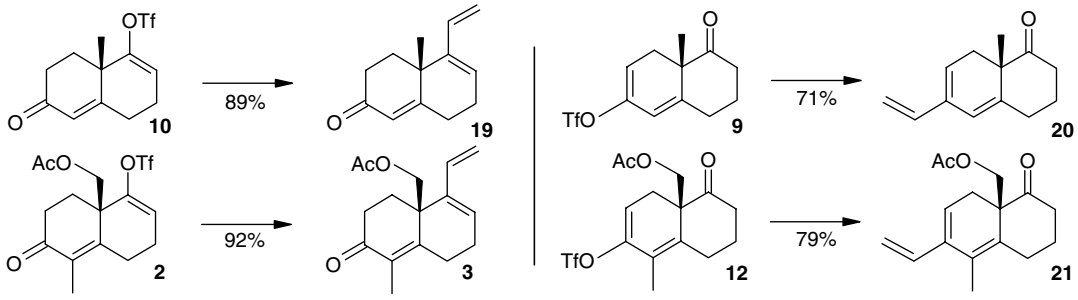

Scheme 6. Reagents and conditions: $Pd_2(dba)_3{\cdot}CHCl_3$ (2.5 mol %), $AsPh_3$ (10 mol %), NMP, vinyl(tributyl)tin (1.1 equiv), rt, 1 h.

Supplementary data

Supplementary material associated with this article contains detailed experimental procedures for the preparation of the enol triflates **2**, **4**, **7**, **9**, **10**, **12**, and the corresponding Stille coupling products with vinyl(tributyl)tin **3**, **5**, **8**, **19**, **20**, **21**, their spectral data (IR, UV, ^{1}H and ^{13}C NMR, MS) and those of the bis-enol triflates **11** and **13**. Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2006.03.185.

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