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Allylation

A Novel Allyl Transfer Coupled with a Grob Fragmentation

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Abstract: A novel acid-promoted rearrangement is disclosed. In the previously unknown transformation, an allyl group migrated to an in situ formed carbocation stabilized by an electron-rich aryl or heteroaryl group, resulting in a stereoselective intramolecular Grob fragmentation. The outcome of the rearrangement observed with an array of substrates can be satisfactorily rationalized using a working hypothesis with the aid of a six-membered transition state similar to those proposed for the anionic oxy-Cope or oxonia-Cope rearrangements, but involving only one instead of two double bonds.

During our total synthesis[1a] of demethyl (C-11) cezomycin, the most recent member in the pyrrol ether family of antibiotics,[1b] it was desired to remove the TBS protecting group in the intermediate **1a** to release a free OH group at the C-6 position (Figure 1). As the functionalities in this simple compound are not particularly unstable according to the existing knowledge, the desilylation was expected to be smooth and clean. However, to our surprise, when commonly employed reagents were used such as nBu$_4$NF, HF or HF·py (always led to a complex product mixture) the reaction failed.

Therefore, we decided to employ *para*-toluenesulfonic acid (*p*TsOH)/MeOH to achieve the desilylation in the absence of any fluoride ions. Under such conditions the composition of the reaction mixture was simpler. However, the only product that could be isolated was **3** instead of the originally expected alcohol **2**. Judging from the reaction conditions employed, the methoxy group at the C-6 in **3** was most likely resulting from solvolysis of an intermediate carbocation at the C-6 formed through either an acid-mediated dehydration of the expected desilylation product **2** or direct removal of a TBSO from the C-6 in **1a**.

Using MeCN-H_2O to replace the MeOH in the reaction to exclude the methanolysis indeed eliminated the formation of **3**. Nevertheless, the only isolatable product (in 50% yield) was, surprisingly, the aldehyde **4a**.[2] More surprisingly, the same aldehyde (**4a**) was also obtained from **1b** under the same conditions, in an even better yield (70%).

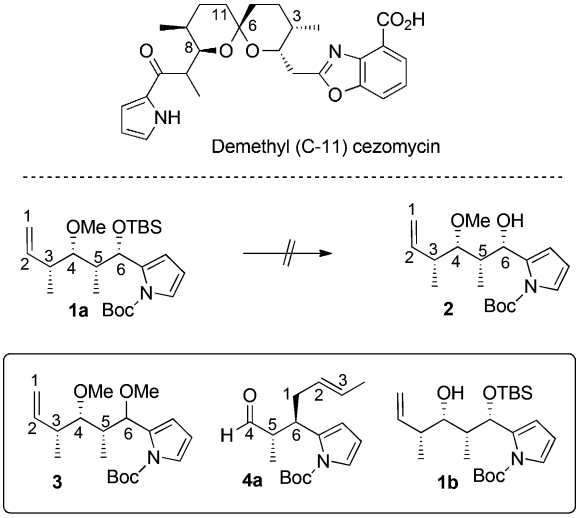

Figure 1. Desilylation of **1a** led to **3** or **4a** instead of **2**; **4a** could also result from **1b**. TBS = *tert*-butyldimethylsilyl; Boc = *tert*-butoxycarbonyl.

Judging from the clean ^{1}H and ^{13}C NMR spectra and the significant optical rotation value ($[\alpha]_D^{22} = +21.5$) for **4a**, what occurred here appeared to be a stereoselective rearrangement, which does not have any apparent precedents to date (to the best of our knowledge). Therefore, further investigations were carried out to gain more information to understand this (then) seemingly very peculiar transformation, such as the pre-requisite for the rearrangement (any other groups at the C-6 position than the pyrrolyl) and the influence of the substrate chirality on the stereochemical outcome of the rearrangement.

To facilitate the study of the less understood reaction, we began with seeking better reaction conditions for the formation of **4a**. Using the more readily attainable **1b** (the synthetic precursor for **1a**) we first performed the reaction in MeCN in the absence of any added H_2O. The same product **4a** was also obtained, but in only 20% yield. Then, we used Et_2O as the reaction solvent. In this case the yield of **4a** pleasingly increased to 85%. Comparable yields were also observed in CH_2Cl_2. Therefore, either Et_2O or CH_2Cl_2 was employed in all following experiments.

The reaction proceeded rather fast at ambient temperature. The reaction was faster when more of the *p*TsOH acid catalyst was added. When equal molar amounts of *p*TsOH were employed, the reaction was complete within just a few minutes.

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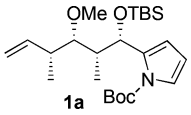
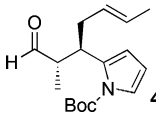
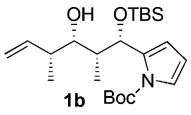
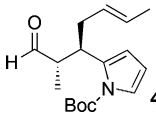
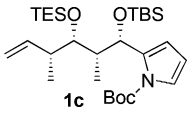
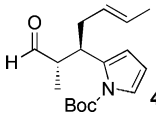
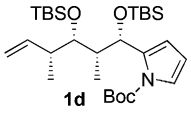
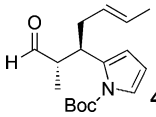
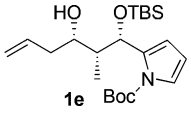
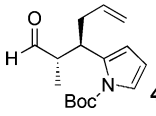
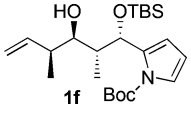
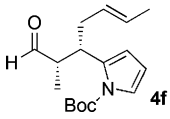
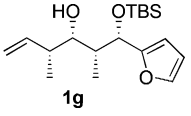
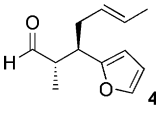
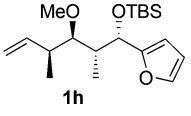
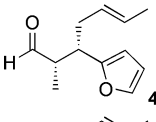
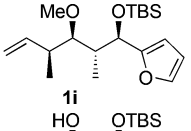
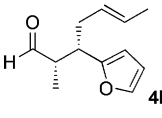
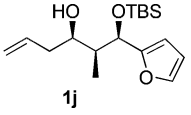
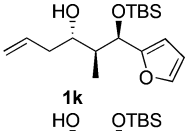
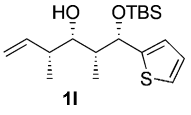
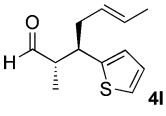
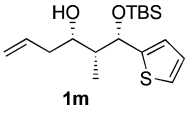
Table 1. Summary of the results with substrates **1a–1f**.[a]

Entry	Substrate	Main Product (yield)
1	 **1a**	 **4a** (79%)
2	 **1b**	 **4a** (85%)
3	 **1c**	 **4a** (61%)
4	 **1d**	 **4a** (46%)
5	 **1e**	 **4e** (60%)
6	 **1f**	 **4f** (83%)

[a] All reactions were performed in Et_2O at ambient temperature in the presence of *p*TsOH. TES = triethylsilyl.

Table 2. Summary of the results with substrates **1g–1m**.[a]

Entry	Substrate	Main Product (yield)
1	 **1g**	 **4g** (83%)
2	 **1h**	 **4h** (83%)
3	 **1i**	 **4h** (61%)
4[b]	 **1j**	No reaction ocurred
5[b]	 **1k**	No reaction ocurred
6[c]	 **1l**	 **4l** (83%)
7	 **1m**	A complicated mixture

[a] All reactions were performed in Et_2O at ambient temperature in the presence of *p*TsOH. [b] The starting material (**1j** or **1k**) was essentially unchanged. [c] Performed in CH_2Cl_2 instead of Et_2O under otherwise the same conditions.

The substrate scope, functional group compatibility, and the influence of the stereochemistry of the substrates were next examined. The pyrrolyl-containing substrates were tested first (Table 1). With or without a protecting group on the C-4 OH, **1a–d** all afforded **4a** as the only isolatable product (Table 1, entries 1–4). However, the yields varied between 46–85%, thereby indicating that the group on the C-4 OH (i.e., H, Me, TES or TBS) had a strong influence on the allyl migration. Compound **1e**, which had no substituent at the C-3 position, also delivered an *anti* aldehyde (**4e**, Table 1, entry 5) as observed with **1a–d**, but the yield was only 60%. Compound **1f**, which had a different relative configuration to that of **1b** at C-4/C-5, gave a different diastereomer **4f** (Table 1, entry 6).

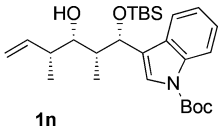
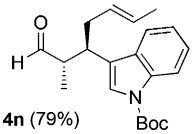
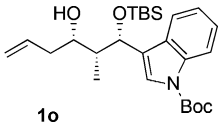
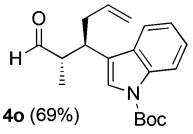
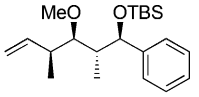
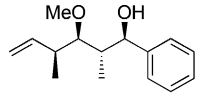
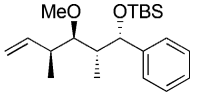
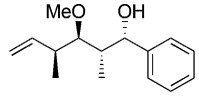
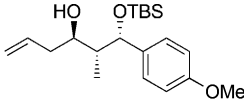
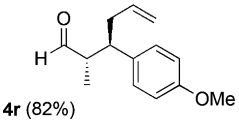
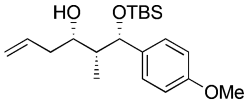
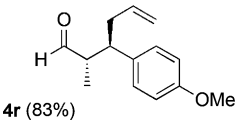
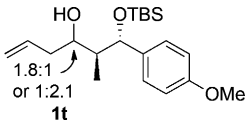
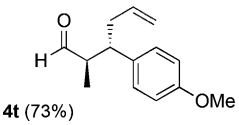
The second group of substrates are shown in Table 2; these substrates have either a furanyl or a thienyl group instead of a pyrrolyl group on the C-6 position. For compounds **1g–i**, similar results (Table 2, entries 1–3) to those observed with **1a–f** were obtained. Again, the configuration of the newly formed C-6 was controlled by the relative configurations of the C-4 and C-5 as in the pyrrolyl cases. It is interesting to note that **1h** and **1i** gave the same product **4h** (Table 2, entries 2 and 3), indicating that the C-6 configuration of the product was not controlled by the C-6 configuration of the substrate. This was consistent with the indication for the formation of a carbocation (planar) mentioned above.

Substrates without the C-3 substituent (**1j** and **1k**) were next tested. Unlike their pyrrolyl counterparts, **1j** and **1k** were essentially fully recovered (only traces/negligible amounts of unidentified side-products were formed) when Et_2O, PhMe or THF were used as the reaction solvent (Table 2, entries 4 and 5). However, when the reaction was run in CH_2Cl_2 or DMF, the reaction outcome was completely different; a complicated product mixture was obtained.

The thienyl-containing substrate (**1l**) also underwent the allyl transfer smoothly, delivering the expected aldehyde **4l** in 83% yield (Table 2, entry 6). However, without the C-3 substituent, the reaction mixture became very complicated (Table 2, entry 7), in sharp contrast to the result with **1e**.

The results with several other substrates are summarized in Table 3. Among these, the indonyl-containing alcohols reacted well, with or without the C-3 methyl group (Table 3, entries 1 and 2). If the C-6 aryl group was a phenyl group rather than a heterocycle, desilylation occurred but no rearrangement took place (Table 3, entries 3 and 4). However, when the phenyl ring had a *p*-methoxy group (**1r** and **1s**), the allyl transfer took place easily even in the absence of a C-3 substituent, thereby affording the same product (**4r**) regardless of the C-4 configuration (Table 3, entries 5 and 6). In addition, **1t** (either a 1:1.8 or a 1:2.1 mixture of the two C-4 epimers) afforded **4t** (the antipode of **4r**) as expected (Table 3, entry 7), confirming that the absolute configuration of **4** depended on the absolute config-

Table 3. Summary of the results with substrates **1n–1t**.[a]

Entry	Substrate	Main Product (yield)
1[b]	 **1n**	 **4n** (79%)
2	 **1o**	 **4o** (69%)
3	 **1p**	 **2p** (100%)
4	 **1q**	 **2q** (100%)
5[b]	 **1r**	 **4r** (82%)
6[b]	 **1s**	 **4r** (83%)
7[c]	 **1t**	 **4t** (73%)

[a] All reactions were performed in Et_2O at ambient temperature in the presence of *p*TsOH. [b] Performed in CH_2Cl_2 instead of Et_2O under otherwise the same conditions. [c] See the Supporting Information (Scheme S10).

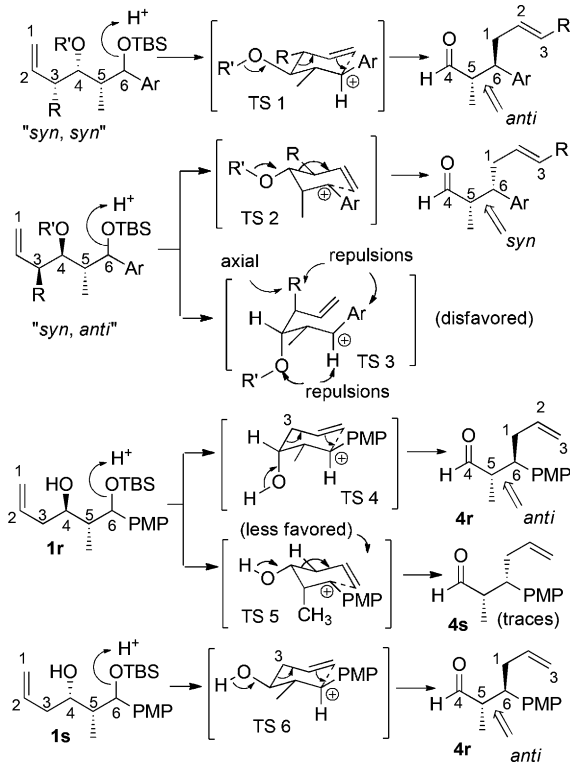


Figure 2. A working hypothesis that may rationalize the outcome of the coupled allyl transfer-Grob fragmentation. The "*syn*,*syn*" and "*syn*,*anti*" relative configurations are referred to the C-3/C-4 and C-4/C-5. Note that the actual mechanism is still to be established.

uration of the C-5 of **1**; the C-4 and C-6 configurations of **1** had no effects on the configuration of the product.

At the present stage no definite mechanism for the observed allyl transfer is available. However, it is possible to rationalize most observations with the aid of a working model/hypothesis. For those substrates of the "*syn*, *syn*" configurations such as **1a–d**, the observed results seem to be compatible with a chair transition state (Figure 2, TS 1) with all substituents in equatorial positions. When the substrates have the "*syn*, *anti*" configurations (such as **1f**), the corresponding chair transition state (TS 3) would have two out of three substituents in axial positions and thus is disfavored. The alternative (TS 2) with only one out of three substituents in an axial position is thus in operation, leading to *syn* products.[3]

The result with **1r** deserves further explanation, because at first sight, formation of **4r** from **1r** seems to have violated the rules derived above. However, in the absence of the C-3 axial substituent, the transition state (Figure 2, TS 4) may be less unstable than the disfavored transition state for the "*syn*,*anti*" substrates (TS 3). Also, the chair with the C-5 CH_3 (larger in size than OH) in an equatorial position (TS 4) is expected to be of lower energy than that with the C-4 OH in an equatorial position (TS 5); that the main product was **4r** rather than **4s** is therefore still reasonable.

To the best of our knowledge, the coupled allyl migration-Grob fragmentation does not have any precedents in the literature. However, it does carry partial resemblance to each of the Cope,[4] oxonia-Cope,[5] or anionic oxy-Cope[6] rearrangement in one aspect or another. Compared with the known rearrangements, a novel feature of the present reaction is that the allyl group is transferred to a carbocation (generated in situ by an acid and stabilized by an aryl group), which is not part of a double bond or an oxocarbenium ion (such as the "-C=O^+-" in the oxonia-Cope reaction). Besides, the Grob fragmentation[7] here is triggered off by an acid-induced carbocation, rather than an alkoxide generated by a strong base as in the anionic oxy-Cope reaction. Thus, despite its partial similarity to each of those known rearrangements, the reaction observed in this study does not fall into any of the existing categories; it represents a new one of its own.[8]

In conclusion, a novel acid-promoted rearrangement has been identified, in which an allyl group migrated to an in situ formed carbocation stabilized by an aryl or heteroaryl group; an electron-rich aryl or heteroaryl group was proven essential for the occurrence of the rearrangement. The rearrangement proceeded rather fast at ambient temperature, delivering an optically active aldehyde with the absolute configuration at

the C-5 position (α to the aldehyde carbonyl group) unchanged. The configuration of the C-6 (β to the carbonyl group) of the product, however, depended on the relative configurations of the substrate. In the presence of a substituent at C-3, the relative configuration of the C-4 in the substrate could affect the outcome of the rearrangement. For those substrates without any substituent at the C-3 position, the configuration of the C-4 practically had no influence on the reaction.

Although the precise mechanism of the newly identified rearrangement is still to be established, the obtained results can be satisfactorily rationalized using a working model/hypothesis with the aid of a six-membered transition state similar to those proposed for the Cope related rearrangements. And despite its partial resemblance to [3,3] sigmatropic rearrangements, this new reaction is different in several aspects: (1) only one double bond is involved, (2) the allyl group is transferred to a carbocation stabilized by an aryl or heteroaryl group, rather than an oxocarbenium (-C=O$^+$-) as in the oxonia-Cope rearrangement,[9] and (3) the Grob fragmentation is not induced by a strong base (as in the anionic oxy-Cope rearrangement) but by an acid.[10]

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Keywords: Aldol reaction · allylation · migration · polyketides · rearrangement

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[2] For the configuration of **4a**, see the Supporting Information.

[3] The *anti*/*syn* ratio for the pyrrols **4a** and **4f** was estimated (by ^{1}H NMR spectroscopy) to be approximately 93:7 and 1:9, respectively, while the corresponding ratio for furans **4g** and **4h** was approximately 9:1 and 1:3, respectively. Other products appeared to be predominated by only one diastereomer. See also Ref. [9]).

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[7] For a recent review, see:M. A. Drahl, M. Manpadi, L. J. Williams, *Angew. Chem. Int. Ed.* **2013**, *52*, 11222 – 11251; *Angew. Chem.* **2013**, *125*, 11430 – 11461. Perhaps the present observations may be described as a homologous Grob fragmentation.

[8] Another way to relate the present reaction to known ones may be Prins-pinacol rearrangement, where the cation adds to the C–C double bond as in a Prins reaction while the fragmentation at the C-4 partially resembles that in a pinacol rearrangement.

[9] For further stereochemical evidence for the rearrangement, see the Supporting Information.

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