New reactions of 2-methylenetetrahydropyrans. A three component coupling protocol for the synthesis of tetrahydropyranyl ketides†

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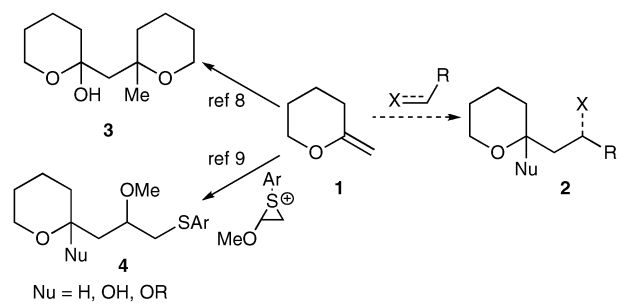
Three component coupling of a 2-methylenetetrahydropyran, an activated aldehyde or ketone and a secondary nucleophile provides an efficient preparation of tetrahydropyranyl ketides, a unit common to many complex natural products.

2-Methylenetetrahydropyrans are useful intermediates for the synthesis of complex molecules.[1] These substrates have been utilized for the preparation of C-glycosides,[2] fused polyethers,[3] spiroketals,[4] and related compounds. Nonetheless, the chemistry of these systems is less developed than that of the corresponding 2,3-dihydropyrans. Efforts to functionalize the exocyclic double bond have largely focused on the introduction of heteroatoms, while protocols for carbon–carbon bond formation, particularly at the terminus, are more limited. Attempts to further elaborate the enol ether include B-alkyl Suzuki coupling,[5] radical processes,[6] and cycloaddition reactions[7] (Scheme 1). Less common are methods that take advantage of the nucleophilic character of the exocyclic enol ether for direct formation of a carbon–carbon bond (**2**). Such examples have been limited to dimerization processes (**3**)[8] and reaction with *epi*-sulfonium ions (**4**).[9] As functionalized tetrahydropyrans are integral components of many biologically significant compounds, the development of more general nucleophilic processes could find broad application in complex molecule synthesis.

Our interest in the synthesis of tetrahydropyran containing polyketide natural products such as spirastrellolide A[10] led us to consider methods for the synthesis of tetrahydropyranyl ketides like **5**. We anticipated that the nucleophilic addition of an exocyclic enol ether **1** to an aldehyde or ketone would give the desired 2-tetrahydropyranylethanol derivative **5** upon reaction of the intermediate oxonium species with a secondary



Scheme 1 C–C bond forming reactions of 2-methylenetetrahydropyrans.

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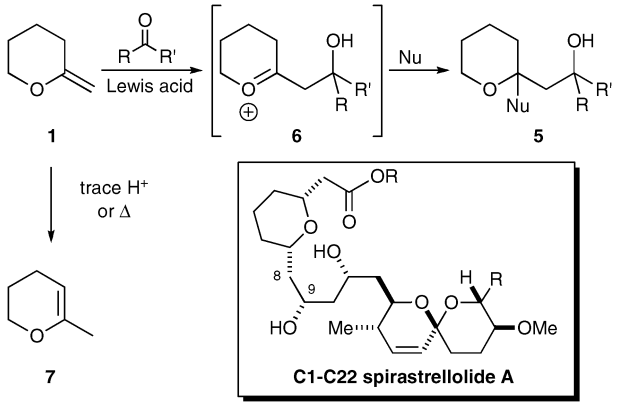
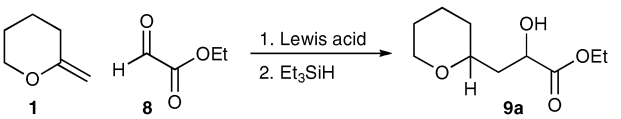


Scheme 2 Proposed synthesis of tetrahydropyranyl ketides **5**.

nucleophile (Scheme 2). Such a process could be used to form the C8–C9 bond of spirastrellolide A. Though this mode of reactivity has previously been reported for 2,3-dihydropyrans,[11] similar reactions for the corresponding exocyclic enol ethers have remained largely unexplored. This omission is likely due to the propensity of these systems to undergo rapid double bond isomerization (**7**) upon heating or in the presence of trace amounts of protic acid. Nonetheless, the requisite exocyclic enol ethers are readily available *via* dehydrohalogenation of a suitably substituted tetrahydropyran[12] or by lactone methylenylation.[13]

In order to evaluate the feasibility of using exocyclic enol ethers in nucleophilic addition processes, we examined the

Table 1 Reaction of enol ether **1** with ethyl glyoxylate **8** and Et_3SiH



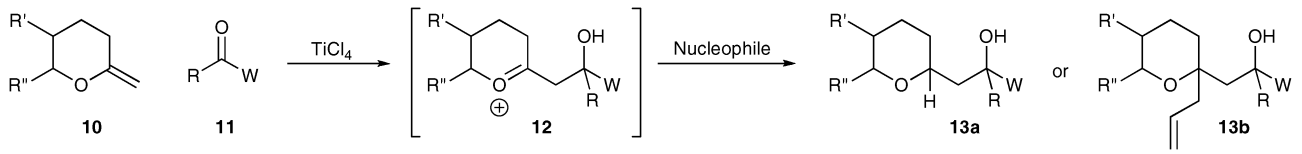
Entry	Ratio **1** : **8**	Lewis acid	Equiv. LA	Time[a]	Yield (%)
1	1 : 1.2	$BF_3{\cdot}OEt_2$	1	1 h	—
2	1 : 1.2	$SnCl_2$	1	1 h	—
3	1 : 1.2	$ZnCl_2$	1	1 h	—
4	1 : 1.2	$EtAlCl_2$	1	1 h	—
5	1 : 1.2	Et_2AlCl	1	1 h	—
6	1 : 1.2	$TiCl_4$	1	1 h	48
7	1.5 : 1	$TiCl_4$	1	1 h	56
8	1 : 1.2	$TiCl_4$	1	20 min	45
9	1 : 1.2	$TiCl_4$	1	10 min	59
10	1 : 1.2	$TiCl_4$	1	—[b]	86
11	1.2 : 1	$TiCl_4$	1	—[b]	84
12	1 : 1.2	$TiCl_4$	0.5	—[b]	45
13	1 : 1.2	$TiCl_4$	0.2	—[b]	23
14	1 : 1.2	$TiCl_4$	0.1	—[b]	10

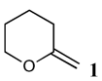
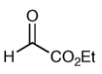
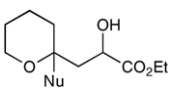
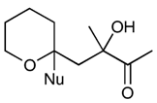
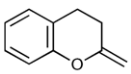
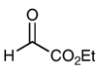
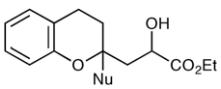
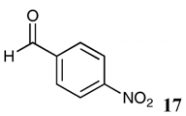
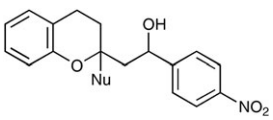
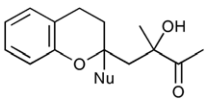
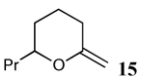
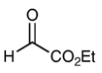
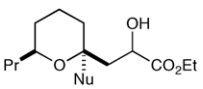
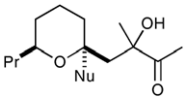
[a] Time reaction mixture stirred prior to addition of Et_3SiH. [b] Et_3SiH added before the Lewis acid.

reaction of enol ether **1**[14] with ethyl glyoxylate **8**[15] using Et_3SiH as the secondary nucleophile (Table 1). Though a variety of Lewis acids were screened in this application, $TiCl_4$ gave the best results providing the desired 2-hydroxy ester **9** in the highest yields and with the fewest side reactions (entries 1–6). Variation in the reaction stoichiometry and time to addition of reducing agent were evaluated in order to optimize yields further. As shown, the relative percentage of reactive components **1** and **8** has little impact on the yield of the reaction (entries 6 and 7, 10 and 11). More important to the success of this transformation is the ready availability of the nucleophile upon generation of the intermediate oxonium species (entries 6, 8–10). Best results are obtained when Et_3SiH is present in the reaction mixture prior to addition of the Lewis acid. In these cases, reduction in the amount of $TiCl_4$ utilized results in a corresponding decrease in the product yield (entries 10, 12–14). Based on these findings, the protocol that unfolds is one in which (1) activation of the aldehyde with equimolar amounts of Lewis acid to facilitate rapid addition of the exocyclic enol ether prior to double bond isomerization, and (2) immediate reaction of the oxonium intermediate thus formed with an appropriate nucleophile to minimize side reactions.

The scope of this transformation was next evaluated by varying both carbonyl and nucleophile components. As shown in Table 2, both 2-methylenetetrahydropyrans (**1** and **15**) and the corresponding chroman derivative (**14**) can be utilized as the enol component in these transformations. Addition of these substrates to activated aldehydes **8** and **17** occurs readily at −78 °C. Both hydride and allyl functions can be subsequently incorporated at the C2 position upon treatment of the intermediate oxonium ion with triethylsilane or allyltrimethylsilane, respectively. Similar reactivity is observed with 2,3-butanedione **16** (entries 3, 9, 13). The resulting aldol equivalents are produced in excellent yields. This reaction is significant in that ketones are typically poor electrophiles in intermolecular aldol reactions because the reaction equilibrium

Table 2 Three component coupling reaction of 2-methylenetetrahydropyrans



Entry	Enol ether	Electrophile	Time[a]	Nucleophile	Product		Nu	dr	Yield (%)
1	 **1**	 **8**	5 min	Et_3SiH		**9a**	H	1 : 1	86
2	**1**	**8**	5 min	$CH_2{=}CHCH_2TMS$		**9b**	$CH_2CH{=}CH_2$	2 : 1	55
3	**1**	 **16**	1 h	Et_3SiH		**18a**	H	4 : 1	79
4	**1**	**16**	1 h	$CH_2{=}CHCH_2TMS$		**18b**	$CH_2CH{=}CH_2$	2 : 1	51
5	 **14**	 **8**	5 min	Et_3SiH		**19a**	H	1.5 : 1	97
6	**14**	**8**	5 min	$CH_2{=}CHCH_2TMS$		**19b**	$CH_2CH{=}CH_2$	1 : 1	96
7	**14**	 **17**	1 h	Et_3SiH		**20a**	H	1 : 1	87
8	**14**	**17**	1 h	$CH_2{=}CHCH_2TMS$		**20b**	$CH_2CH{=}CH_2$	1 : 1	97
9	**14**	 **16**	1 h	Et_3SiH		**21a**	H	5 : 1	95
10	**14**	**16**	1 h	$CH_2{=}CHCH_2TMS$		**21b**	$CH_2CH{=}CH_2$	1 : 1	97
11	 **15**	 **8**	5 min	Et_3SiH		**22a**	H	5 : 1	77
12	**15**	**8**	5 min	$CH_2{=}CHCH_2TMS$		**22b**	$CH_2CH{=}CH_2$	1 : 1	67
13	**15**	 **16**	1 h	Et_3SiH		**23**	H	2 : 1	56

[a] Time before secondary nucleophile addition.

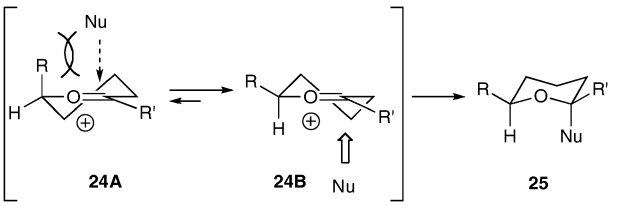


Fig. 1 Stereochemistry of nucleophile addition.

lies far to the left. Further, use of a ketone electrophile provides access to compounds that contain a quaternary center β to the tetrahydropyran ring. When allyltrimethylsilane is used as the secondary nucleophile (entries 4, 10), two oxygenated quaternary centers are generated in a single process.

In cases where a pre-existing stereocenter is present at C6 of the tetrahydropyran, the three component coupling proceeds to give the corresponding 2,6-*cis*-tetrahydropyrans as the only isolated products (entries 11–13). The stereochemistry of these compounds **22** and **23** was determined by nOe. The observed stereoselectivity can be rationalized as shown in Fig. 1. The observed stereoselectivity is consistent with addition of the secondary nucleophile to an oxonium ion intermediate that exists in a half-chair conformation in which the C6 substituent is pseudo-equatorial (**24B**).[16] Subsequent axial attack of the nucleophile is then anticipated on both steric and stereoelectronic grounds.[17] Similar selectivity is observed in the addition of nucleophiles to related tetrahydropyranyl oxonium species.[18]

In conclusion, we have demonstrated a facile synthesis of tetrahydropyranyl ketide derivatives using a three component coupling protocol. These studies demonstrate that 2-methylene-tetrahydropyrans are suitable nucleophiles for addition to activated aldehydes and ketones. Competing double bond isomerization is not a factor. The resulting 2-(tetrahydropyran-2-yl)-alcohols will be useful intermediates for complex molecule synthesis. Current efforts are aimed at the synthesis of spirastrellolide A and related polyketide natural products. These studies will be reported in due course.

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