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Diastereoselective construction of *cis* 2,6-disubstituted tetrahydropyran rings via $In(OTf)_3$-catalyzed intramolecular 2,5-oxonium-ene cyclization: synthetic studies towards the total synthesis of zampanolide and dactylolide

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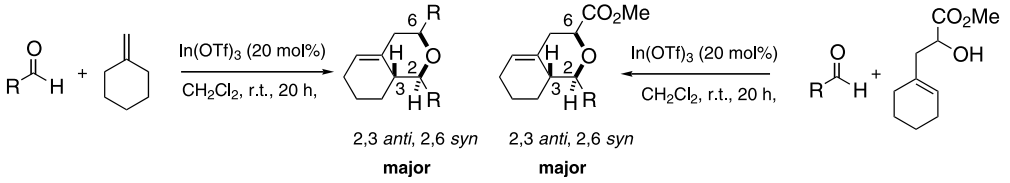
Abstract—Diastereoselective construction of 2,6-disubstituted tetrahydropyrans with an exocyclic double bond was achieved via the $In(OTf)_3$-catalyzed intramolecular 2,5-oxonium-ene cyclization. Its application was further demonstrated by the synthesis of a common intermediate for both zampanolide and dactylolide, fragment **I**, with a total yield of 42% in three steps starting from (2*E*)-3-bromobut-2-enal.

Recently, our group revealed that $In(OTf)_3$ is an efficient Lewis acid for the in situ formation of oxonium ions from homoallylic alcohols and aldehydes.[1–5] As a further application of $In(OTf)_3$, we and others have developed an atom-economic and efficient construction of tetrahydropyran rings via intramolecular 2,5-oxonium-ene cyclization (Scheme 1).[6–9] Recently, Smith and co-workers completed the total synthesis of (+)-dactylolide[10] and (+)-zampanolide,[11] both of which feature a *cis* 2,6-disubstituted tetrahydropyran[12] with an exocyclic double bond (Fig. 1). Attracted by this interesting structure, we decided to explore the construction of *cis* 2,6-disubstituted tetrahydropyrans with an exocyclic double bond utilizing the $In(OTf)_3$-catalyzed intramolecular 2,5-oxonium-ene cyclization of homoallylic alcohols with a terminal double bond and aldehydes, as well as the application of this methodology to the diastereoselective construction of fragment **I**, a common intermediate for the total synthesis of dactylolide and zampanolide.[10,11]

We initiated our study by synthesizing a series of homoallylic alcohols **1**. An efficient and easy access towards these is the indium-mediated allylation reaction,[13] through which a variety of homoallylic alcohols were obtained (Scheme 2).

With homoallylic alcohols in hand, we investigated the cyclization reaction by employing **1a** and benzaldehyde as substrates (Eq. (1)). When benzaldehyde (0.6 mmol) was treated with **1a** (0.5 mmol) in the presence of $In(OTf)_3$ (0.1 mmol) in CH_2Cl_2 (1.5 mL) at 0°C, the desired cyclization product was isolated in a 35% yield together with 50% of an unidentified by-product (Table 1, entry 1). Further optimization of the reaction conditions revealed that mixing the benzaldehyde (0.5 mmol) and **1a** (1 mmol) in CH_2Cl_2 (1.5 mL) at 0°C followed by addition of $In(OTf)_3$ (0.1 mmol) increased the yield of the cyclization product to 80% with very good diastereoselectivity (95:5) (Table 1, entry 2).



Scheme 1.

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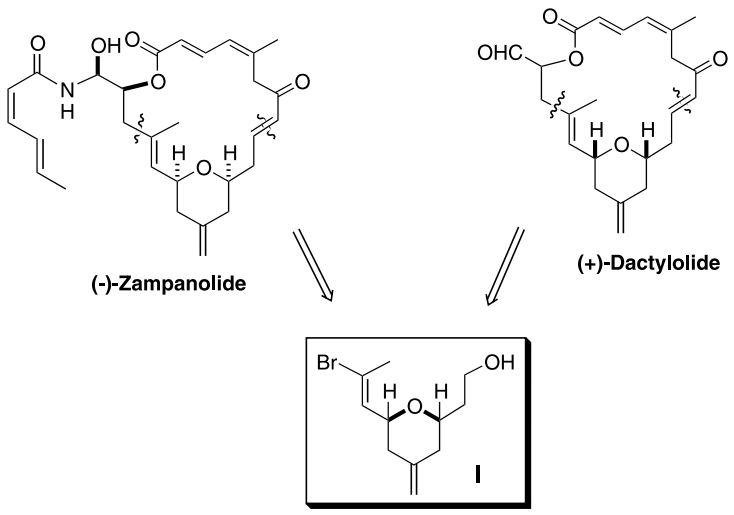
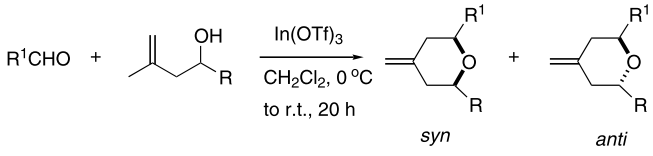
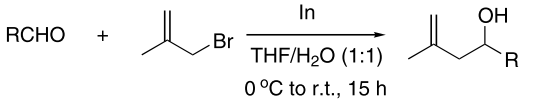


Figure 1.



(1)



1a: R = Ph (90%) **1c**: R = $(CH_3)_2C{=}CH$ (77%)
1b: R = CO_2Me (70%) **1d**: R = $TBDPSOCH_2CH_2$ (95%)

Scheme 2.

With this exhilarating result, we extended this method to a variety of aldehydes and homoallylic alcohols. In all cases, the yields were moderate to excellent, while the diastereoselectivities were substrate dependent. For homoallylic alcohol **1a**, the reactions proceeded elegantly for both aromatic and aliphatic aldehydes, producing the cyclization products in excellent yields and good diastereoselectivities (Table 1, entries 2 and 3). Considering the versatility of the methyl ester functional group in organic synthesis, homoallylic alcohol **1b** was employed as an olefin resource. However, the diastereoselectivities in most cases were poor (Table 1, entries 5, 6 and 7), with hydrocinnamaldehyde being an exception (Table 1, entry 4). In order to apply this methodology to natural product synthesis, the reaction of homoallylic alcohol **1d**, a prerequisite for the assembly of fragment **I**, and a variety of aldehydes (conjugated, aromatic as well as aliphatic) were next examined carefully. It was found that both conjugated and aromatic aldehydes can react with **1d** smoothly to give the expected products in moderate yields and good diastereoselectivities (Table 1, entries 9, 10, 12 and 13). Although the yield for aliphatic aldehydes is good, the diastereoselectivity is much lower (Table 1, entry 11). For comparison, we also synthesized compound **8** from homoallylic alcohol **1c** and aldehyde **1e**, and both a comparable yield and diastereoselectivity were obtained.

Table 1. $In(OTf)_3$-catalyzed oxonium-ene cyclization of homoallylic alcohols and aldehydes

Entry	R^1CHO	Homoallylic alcohol	Product (%)[c,d] *syn*:*anti*[e]
1[a]	Ph	**1a**	**2** (35)/–
2[b]	Ph	**1a**	**2** (80)/95:5
3	$CH_3(CH_2)_4$	**1a**	**3** (85)/81:19
4	$PhCH_2CH_2$	**1b**	**4** (90)/84:16
5	$CH_3(CH_2)_4$	**1b**	**5** (70)/66:34
6	*c*-hex	**1b**	**6** (72)/58:42
7	Ph	**1b**	**7** (52)/58:42
8	$TBDPSO(CH_2)_2$	**1c**	**8** (50)/82:18
9	$(CH_3)_2C{=}CH$	**1d**	**8** (52)/80:20
10	$PhCH{=}CH$	**1d**	**9** (90)/75:25
11	$PhCH_2CH_2$	**1d**	**10** (65)/56:44
12	$CH_3C{=}C(CH_3)$	**1d**	**11** (55)/75:25
13	Ph	**1d**	**12** (80)/74:26

[a] To a suspension of $In(OTf)_3$ (0.1 mmol) in CH_2Cl_2 (1.5 mL) was added benzaldehyde (0.6 mmol) followed by **1a** (0.5 mmol) at 0°C.
[b] To a solution of benzaldehyde (0.5 mmol) and **1a** (1 mmol) in CH_2Cl_2 (1.5 mL) was added $In(OTf)_3$ (0.1 mmol) at 0°C.
[c] Yield after flash column chromatography.
[d] Unidentified by-product was also isolated in the range of 7–50%.
[e] Determined by ^1H NMR.

The relative stereochemical outcome of the intramolecular 2,5-oxonium-ene cyclization was established by ^1H and ^{13}C NMR studies of product **2** in which the *syn* isomer is a *meso* compound. The stereochemistries of the other cyclization products were determined based

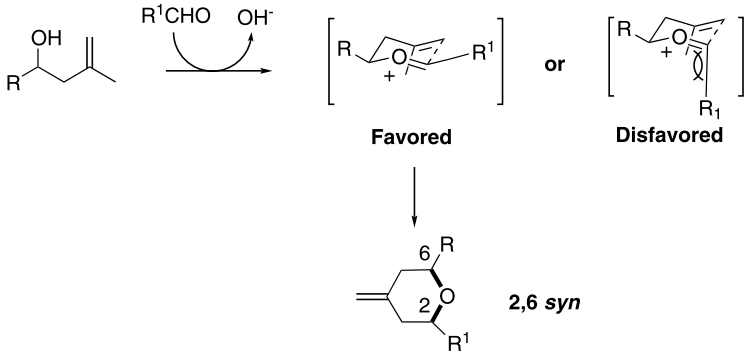
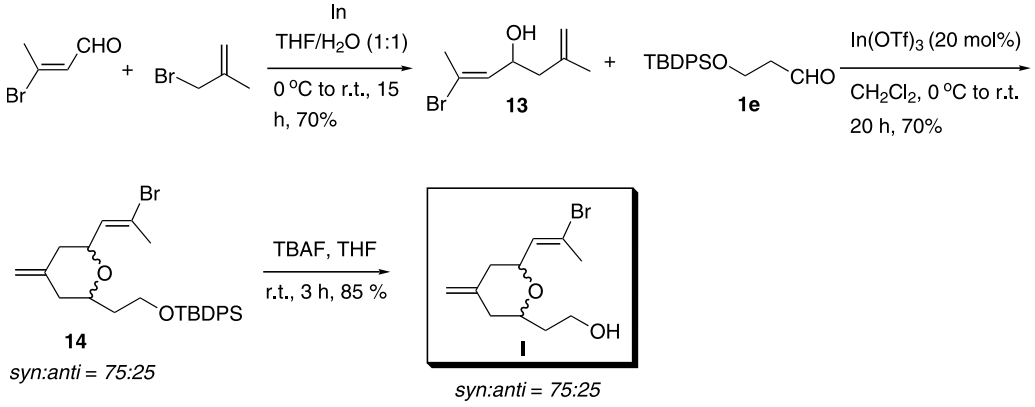


Figure 2.



Scheme 3.

on ^{1}H and ^{13}C NMR spectral similarities. The observed predominant 2,6 *syn* selectivity can be rationalized by the cyclic six-membered chair-like transition state favoring an all-equatorial substitution pattern (Fig. 2).

Encouraged by the above results, we started to explore the construction of fragment **I**, a common intermediate for both dactylolide and zampanolide. As outlined in Scheme 3, our synthesis commenced with the indium-mediated allylation of (2*E*)-3-bromobut-2-enal[14] with 3-bromo-2-methyl propene, which afforded the homoallylic alcohol **13** in 70% isolated yield. $In(OTf)_3$-catalyzed intramolecular 2,5-oxonium-ene cyclization of **13** and aldehyde **1e**[15] successfully provided the desired cyclization product **14** in 70% isolated yield with good *syn* diastereoselectivity (75:25). Finally, treatment of **14** with TBAF finished the construction of fragment **I** as two inseparable isomers in three steps with a total yield of 42% starting from (2*E*)-3-bromobut-2-enal. From the 500 MHz ^{1}H NMR spectrum of **I**, the major *syn* isomer is in accordance with that of the literature,[11] which further demonstrated the stereochemical outcome of the $In(OTf)_3$ intramolecular 2,5-oxonium-ene cyclization.

In summary, an atom-economic, efficient and highly diastereoselective construction of tetrahydropyran rings has been achieved via the $In(OTf)_3$-catalyzed intramolecular 2,5-oxonium-ene cyclization. Using this methodology, a common intermediate of both dactylolide and zampanolide was elegantly constructed in only three steps starting from (2*E*)-3-bromobut-2-enal with a total yield of 42% and high *syn* diastereoselectivity. In view of the easy availability of chiral homoallylic alcohols, this method will provide an easy access towards enantioselective construction of tetrahydropyran rings. A study along this direction is in progress.

Acknowledgements

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