Natural Product Synthesis

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Stereoselective Synthesis of 2,6-*cis*-Tetrahydropyrans through a Tandem Allylic Oxidation/Oxa-Michael Reaction Promoted by the *gem*-Disubstituent Effect: Synthesis of (+)-Neopeltolide Macrolactone**

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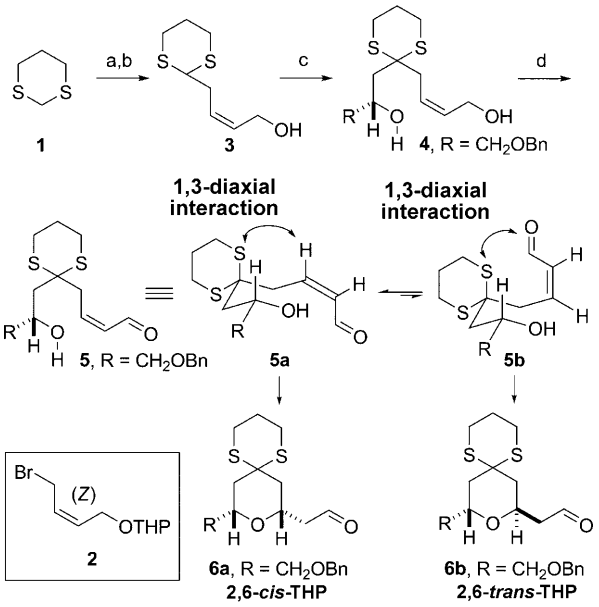
Structurally complex tetrahydropyrans (THPs) are found in a wide range of biologically interesting natural products. Although considerable effort has been devoted to the development of synthetic routes to THPs,[1] there still exists a great need for a synthetic approach to these classes of molecules that enables rapid and easy access to substrates, proceeds with excellent stereoselectivity in excellent yield, and requires mild reaction conditions compatible with various functional groups.

Surprisingly, despite considerable progress in the Michael reaction of carbon nucleophiles, there has been far less interest in the analogous Michael reaction of oxygen nucleophiles (oxa-Michael reaction). The slow development of the oxa-Michael reaction is mainly due to major drawbacks such as the low reactivity of oxygen nucleophiles and the reversibility issue, as well as a lack of control over stereoselectivity.[2] Owing to the poor nucleophilicity of oxygen atoms in the oxa-Michael reaction, alcohols must be deprotonated by strong bases to enhance their nucleophilicity, or the conjugate acceptor must be activated by Lewis or Brønsted acids, amines, or transition-metal complexes.[2–4] These harsh reaction conditions are often incompatible with other functional groups of the substrate. In particular, as a result of competitive acetal formation, instability, and the enolizability of aldehydes, the oxa-Michael reaction of alcohols to α,β-unsaturated aldehydes has been elusive.[5]

Herein, we report the stereoselective and efficient synthesis of 2,6-*cis*-THPs through an unprecedented tandem allylic oxidation/oxa-Michael addition of alcohols to α,β-unsaturated aldehydes promoted by the *gem*-disubstituent effect and its application to the concise synthesis of (+)-neopeltolide macrolactone.

To overcome the low reactivity of oxygen nucleophiles, we envisioned the introduction of a structural element that would promote preorganization of the conformation of a substrate for an intramolecular oxa-Michael reaction. We also anticipated that this structural element could help decrease the reversibility of the reaction to form the oxa-Michael product. We hypothesized that a 1,3-dithiane group at the C4 position of an alcohol nucleophile could satisfy these requirements on the basis of the *gem*-disubstituent effect. Furthermore, the 1,3-dithiane group would serve as a latent functional group for a carbonyl, hydroxy, or olefinic group, or a hydrogen atom.

To test this hypothesis, we prepared substrate **4** for the oxa-Michael reaction as follows (Scheme 1): The 1,3-dithiane coupling[6] of **1** with allyl bromide **2**,[7] followed by THP deprotection, provided **3**. The coupling of **3** with (±)-glycidyl benzyl ether then proceeded smoothly to afford the allylic alcohol **4**. As expected, the chemoselective oxidation of **4** with MnO_2 and subsequent intramolecular oxa-Michael reaction of the resulting α,β-unsaturated aldehyde **5** provided the desired 2,6-*cis*-THP **6a** with excellent stereoselectivity (d.r.>20:1, 93%; tandem allylic oxidation/oxa-Michael reaction).[8–10]



Scheme 1. Synthesis of the 2,6-*cis*-THP **6a** through a tandem allylic oxidation/oxa-Michael reaction: a) *n*BuLi, THF, −78 °C, 1 h, then **2**, −78 °C, 1 h; b) *p*-toluenesulfonic acid, MeOH, 25 °C, 12 h, 78% for two steps; c) *t*BuLi, HMPA/THF (1:10), −78 °C, 5 min, then (±)-glycidyl benzyl ether, −78 °C, 1 h, 83%; d) MnO_2, CH_2Cl_2, 25 °C, 24 h, 93%. Bn = benzyl, HMPA = hexamethylphosphoramide.

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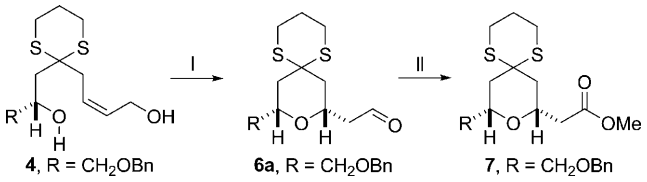
The stereochemical outcome of this tandem allylic oxidation/oxa-Michael reaction can be rationalized on the basis that the unfavorable 1,3-diaxial interaction of the C6 α,β-unsaturated carbonyl group and the C4 dithiane group in conformation **5b** is larger than that of the C6 hydrogen atom and the dithiane group in conformation **5a**; thus, **6a** is formed preferentially. It is known that a 2,6-*cis*-THP is thermodynamically more favorable than a 2,6-*trans*-THP in equilibrium.[11] To identify the origin of the stereoselective formation of **6a** in the tandem reaction, the *trans* isomer **6b** was subjected to the reaction conditions for the cyclization (MnO_2, CH_2Cl_2, 25 °C, 24 h). As no formation of **6a** was observed in this case, we could conclude that the formation of **6a** was kinetically controlled (see the Supporting Information for details).

Encouraged by the preliminary results, we set out to explore the scope of the tandem allylic oxidation/oxa-Michael reaction. First, we examined a range of oxidation conditions for the tandem reaction. The Parikh–Doering oxidation of **4** (SO_3·pyridine, Et_3N/dimethyl sulfoxide (DMSO)/CH_2Cl_2 (1:1:4), 25 °C, 24 h) provided the desired 2,6-*cis*-THP **6a** with excellent stereoselectivity (d.r. > 20:1, 93 %). Other oxidation conditions (pyridinium chlorochromate, tetrapropylammonium perruthenate, or Dess–Martin periodinane) also afforded **6a** (d.r. > 20:1), but in low to moderate yields (21–51 %) owing to competitive oxidation of the secondary hydroxy group, decomposition of the aldehyde intermediate, or possible oxidation of the 1,3-dithiane group. Swern oxidation of **4** did not provide **6a**, but significant decomposition of the aldehyde intermediate was observed (see the Supporting Information for details).

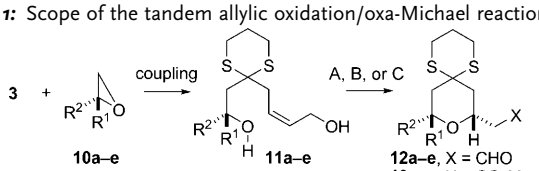
When **4** was subjected to the conditions for the tandem reaction in the presence of dimethyltriazolium iodide,[12] the THP methyl ester **7** was obtained in a single step from **4** in a one-pot allylic oxidation/oxa-Michael/oxidation reaction (Scheme 2). This MnO_2 oxidation catalyzed by an N-heterocyclic carbene proved to be a reliable method for the oxidation of aldehydes containing sensitive electron-rich sulfur atoms to the corresponding carboxylic acids or esters.[13]



Scheme 2. One-pot allylic oxidation/oxa-Michael/oxidation reaction to give the THP ester **7**: I) MnO_2, CH_2Cl_2, 25 °C, 1.5 h; II) dimethyltriazolium iodide, MnO_2, DBU, MeOH, 4 Å MS, 25 °C, 23 h, 61 %. DBU = 1,8-diazabicyclo[5.4.0]undec-7-ene.

To investigate the scope and stereochemical outcome of the tandem reaction with respect to substituents at the C2 position, we prepared allylic alcohols **11a–e** by coupling **3** with the commercially or readily available epoxides **10a–e** and subjected them to MnO_2 or Parikh–Doering oxidation, or MnO_2 oxidation in the presence of dimethyltriazolium iodide (Table 1). The tandem reaction of **11a–d** under the reaction conditions examined proceeded smoothly to provide the corresponding 2,6-*cis*-THP aldehydes **12a–d** or esters **13a–d** with excellent diastereoselectivity (d.r. > 20:1; Table 1, entries 1–4). Even the sterically hindered tertiary alcohol **11e** was converted into the THP aldehyde **12e** and ester **13e** in good yield (75–87 %) under the mild reaction conditions (Table 1, entry 5).

Table 1: Scope of the tandem allylic oxidation/oxa-Michael reaction.



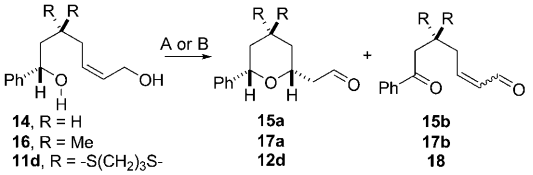
10a, R^1 = H, R^2 = Et
10b, R^1 = H, R^2 = *i*Pr
10c, R^1 = H, R^2 = $C(CH_3)_2CH_2OBn$
10d, R^1 = H, R^2 = Ph
10e, R^1 = Me, R^2 = Me

Entry	Substrate (yield [%])[a]	Conditions[b]	Product (yield [%], d.r.[c])
1	**11a** (74)	A	**12a** (88, > 20:1)
		B	**12a** (87, > 20:1)
		C	**13a** (86, > 20:1)
2	**11b** (72)	A	**12b** (75, > 20:1)
		B	**12b** (87, > 20:1)
		C	**13b** (81, > 20:1)
3	**11c** (76)	A	**12c** (81, > 20:1)
		B	**12c** (75, > 20:1)
		C	**13c** (76, > 20:1)
4	**11d** (83)	A	**12d** (96, > 20:1)
		B	**12d** (94, > 20:1)
		C	**13d** (76, > 20:1)
5	**11e** (67)	A	**12e** (86, NA[d])
		B	**12e** (87, NA[d])
		C	**13e** (75, NA[d])

[a] Yield of isolated **11** from the coupling reaction (*t*BuLi, HMPA/THF (1:10), −78 °C, 5 min, then **10**, −78 °C, 0.5–2 h). [b] A) MnO_2, CH_2Cl_2, 25 °C, 24 h; B) SO_3·pyridine, Et_3N/DMSO/CH_2Cl_2 (1:1:4), 25 °C, 24 h; C) I MnO_2, CH_2Cl_2, 25 °C, 1.5 h; II dimethyltriazolium iodide, MnO_2, DBU, MeOH, 4 Å MS, 25 °C, 23 h. [c] The diastereomeric ratio (2,6-*cis*-THP/2,6-*trans*-THP) was determined by integration of the ^{1}H NMR spectrum of the crude product. [d] Not applicable.

We hypothesized that the 1,3-dithiane group would be critical to overcoming the low reactivity of oxygen nucleophiles and the reversibility of the reaction by promoting an ideal conformation for cyclization through the *gem*-disubstituent effect.[14] To prove this hypothesis, we prepared substrates **14** and **16** with no or a diminished *gem*-disubstituent effect and subjected them to the reaction conditions for the tandem reaction (Table 2). Although the MnO_2 oxidation of **14** provided the desired 2,6-*cis*-THP **15a** (d.r. 7:1; Table 2, entry 1), the reaction also produced ketone **15b** (**15a**/**15b** 3:1) as a result of a slow oxa-Michael addition step owing to the absence of the *gem*-disubstituent effect and the competing oxidation of the benzylic hydroxy group. Parikh–Doering oxidation of **14** failed to provide **15a**; instead, the exclusive formation of **15b** was observed (Table 2, entry 2). When *gem*-dimethyl substitution was introduced in the substrate **14**, the tandem reaction was accelerated (Table 2, entries 3 and 4). Thus, the reaction of **16** with MnO_2 or under Parikh–Doering conditions provided **17a** with good stereoselectivity

Table 2: Investigation of the *gem*-disubstituent effect on reaction rate and stereoselectivity.



14, R = H
16, R = Me
11d, R = -S(CH$_2$)$_3$S-

15a
17a
12d

15b
17b
18

Entry	Substrate	Conditions[a]	Product (yield [%],[b] d.r.[c])
1	**14**	A	**15a**/**15b** 3:1 (83, 7:1)
2		B	**15b** only (92, NA[d])
3	**16**	A	**17a**/**17b** 4:1 (94, 10:1)
4		B	**17a**/**17b** 3:1 (94, 10:1)
5	**11d**	A	**12d** only (96, >20:1)
6		B	**12d** only (94, >20:1)

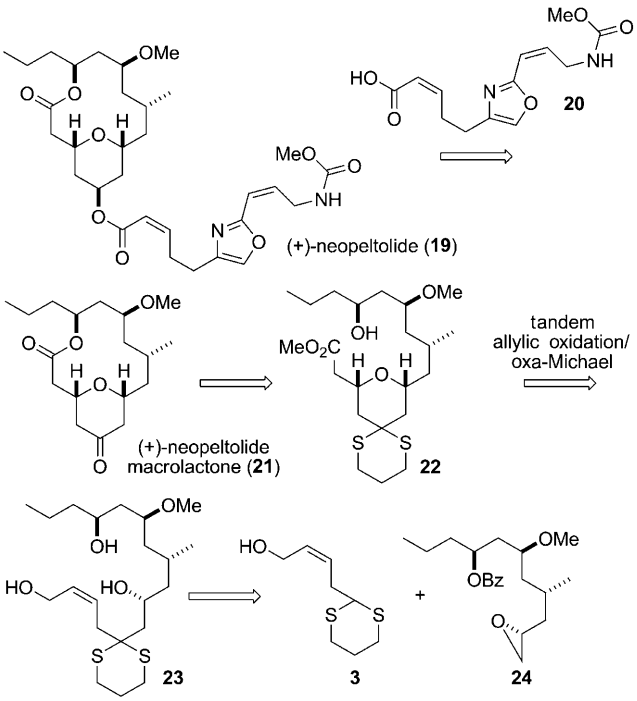
[a] A) MnO_2, CH_2Cl_2, 25 °C, 24 h; B) SO_3·pyridine, Et_3N/DMSO/CH_2Cl_2 (1:1:4), 25 °C, 24 h. [b] Combined yield of the isolated THP and ketone. [c] The diastereomeric ratio (2,6-*cis*-THP/2,6-*trans*-THP) was determined by integration of the ^{1}H NMR spectrum of the crude product. [d] Not applicable.

(d.r. 10:1). However, competing benzylic oxidation was also observed (**17a**/**17b** 4:1 and 3:1, respectively). The oxidation of **11d**, which contains the 1,3-dithiane group, with MnO_2 or under Parikh–Doering conditions gave **12d** with excellent stereoselectivity (d.r. > 20:1) and did not produce **18** (Table 2, entries 5 and 6). These results clearly demonstrated that the *gem*-disubstituent effect accelerated the intramolecular oxa-Michael reaction. A more dramatic *gem*-disubstituent effect was observed when the Parikh–Doering conditions were used. Interestingly, an improvement in stereoselectivity was also observed with the 1,3-dithiane group. This improvement may be due to the increased 1,3-diaxial interaction/more rigid chair-like transition state induced by the cyclic dithiane group compared with the hydrogen atoms or the dimethyl group.

Encouraged by the efficiency and versatility of the tandem allylic oxidation/oxa-Michael reaction, we embarked on a stereoselective synthesis of (+)-neopeltolide macrolactone (**21**). The marine macrolide (+)-neopeltolide (**19**) is an extremely potent inhibitor of tumor-cell proliferation[15] and has attracted considerable interest from a number of synthetic research groups.[16–18] We envisioned that the embedded 2,6-*cis*-4-hydroxy-THP could be constructed by using the tandem allylic oxidation/oxa-Michael reaction as the key bond-forming step (Scheme 3).

The synthesis of **21** started with the preparation of the chiral epoxide **24** for dithiane coupling (Scheme 4). The coupling of **1** with (*R*)-5-iodo-4-methylpentene,[19] followed by the ring opening of (*R*)-(−)-epichlorohydrin and concurrent epoxide formation, afforded **26**. The ring opening of epoxide **26**, deprotection of the 1,3-dithiane group, and Evans–Tischenko reduction[20] of β-hydroxyketone **28** afforded the desired *anti* 1,3-diol **29**. Methylation of the secondary hydroxy group,[21] asymmetric dihydroxylation,[22] and epoxide formation[23] afforded the substrate **24** for the second 1,3-dithiane coupling.

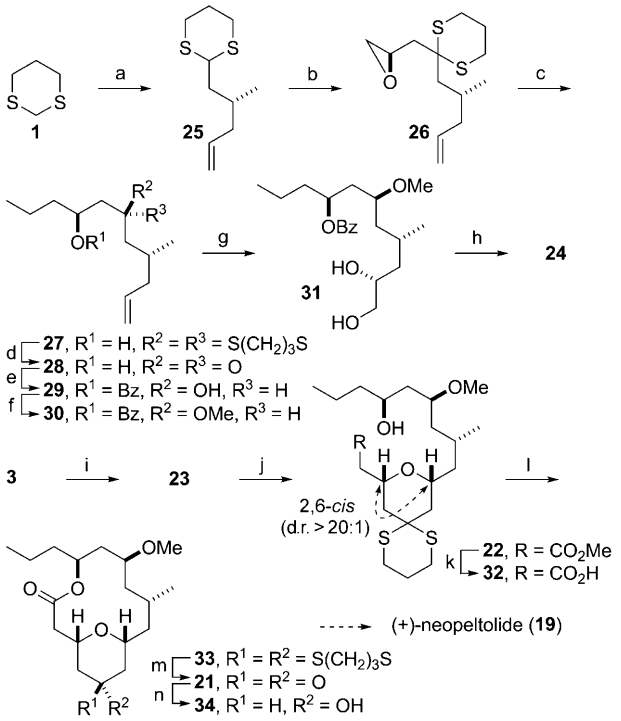
The coupling of **3** and **24** proceeded smoothly with accompanying deprotection of the benzoyl-protected hydroxy group to set the stage for the key tandem allylic oxidation/



Scheme 3. Retrosynthesis of (+)-neopeltolide macrolactone (**21**). Bz = benzoyl.

oxa-Michael reaction. The allylic oxidation/oxa-Michael reaction/oxidation of **23** (MnO_2, CH_2Cl_2, 25 °C, 3 h; then dimethyl triazolium iodide, MnO_2, DBU, MeOH, M.S. (4 Å), 25 °C, 21 h) afforded the desired 2,6-*cis*-THP methyl ester **22** with excellent stereoselectivity (d.r. > 20:1, 78%). The tandem reaction was chemoselective; it did not require any protection of the three hydroxy groups in **23**. The hydrolysis of **22** under basic conditions, followed by a macrocyclization reaction of the resulting acid **32** according to the procedure described by Shiina et al.,[24] proceeded smoothly to give **33**. Final deprotection of the 1,3-dithiane group completed the synthesis of (+)-neopeltolide macrolactone (**21**), which proved identical in all respects to known synthetic **21**.[17b,18e,h] Compound **21** was converted into the known alcohol **34**[17b,18a,c,e,f,g] by a stereoselective reduction.[17b] The synthesis of (+)-neopeltolide (**19**) could be completed by a Mitsunobu esterification reaction of **34** with the known acid **20**,[18f,25] as described previously.[17b,18a,c,e,f,g]

In summary, we have explored a tandem allylic oxidation/oxa-Michael reaction for the stereoselective and efficient synthesis of 2,6-*cis*-THPs. The reaction required no activation of the oxygen nucleophile or aldehyde, was applicable to a broad range of substrates, and proceeded with excellent stereoselectivity. We also demonstrated that the 1,3-dithiane group enabled rapid access to substrates, promoted the intramolecular oxa-Michael reaction through the *gem*-disubstituent effect, and improved the stereoselectivity of the reaction as a result of the increased 1,3-diaxial interaction. The chemoselective nature of the tandem allylic oxidation/oxa-Michael reaction and the efficiency of dithiane coupling reactions enabled a concise and efficient synthesis of (+)-neopeltolide macrolactone (**21**) with minimal use of



Scheme 4. Stereoselective synthesis of the 2,6-*cis*-THP **22** and (+)-neopeltolide macrolactone (**21**): a) *n*BuLi, THF, −78→−10 °C, 1 h, then (*R*)-5-iodo-4-methylpentene, −78→−40 °C, 4 h, 79%; b) *n*BuLi, THF, 25 °C, 5 min, then (*R*)-epichlorohydrin, −78 °C, 2 h, then 25 °C, 12 h, 83%; c) EtMgBr, CuI, THF, −40→−10 °C, 3 h, 96%; d) MeI, $CaCO_3$, CH_3CN/H_2O (3:1), 25 °C, 14 h, 87%; e) PhCHO, SmI_2, THF, 0 °C, 3 h, 87%; f) 1,8-bis(dimethylamino)naphthalene, $Me_3O{\cdot}BF_4$, CH_2Cl_2, 0–25 °C, 2 h, 93%; g) AD mix-β, H_2O/*t*BuOH (1:1), 0 °C, 10 h, 92%, α/β 3:1; h) NaH, *N*-*p*-toluenesulfonylimidazole, THF, 0–25 °C, 1 h, 92%; i) *t*BuLi, HMPA/THF (1:10), −78 °C, 5 min, then **24**, −78 °C, 3 h, 75%; j) MnO_2, CH_2Cl_2, 25 °C, 3 h, then dimethyltriazolium iodide, MnO_2, DBU, MeOH, 4 Å MS, 25 °C, 21 h, 78%; k) 0.1 N LiOH, THF/MeOH (3:1), 25 °C, 1 h, 99%; l) 2-methyl-6-nitrobenzoic anhydride, 4-dimethylaminopyridine, CH_2Cl_2, 24 h, 69%; m) MeI, $CaCO_3$, CH_3CN/H_2O (3:1), 25 °C, 30 h, 89%; n) $NaBH_4$, MeOH, 0 °C, 1 h, 93%.

protecting groups (16 steps to (+)-neopeltolide macrolactone (**21**) in 5.2% overall yield from commercially available (*S*)-(+)-4-isopropyl-3-propionyl-2-oxazolidinone).[26] This synthetic method would be broadly applicable to the efficient synthesis of a diverse set of bioactive natural products containing 2,6-*cis*-THP rings.

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