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# Stereoselective Synthesis of Tetrahydropyrans through Tandem and Organocatalytic Oxa-Michael Reactions: Synthesis of the Tetrahydropyran Cores of *ent*-(+)-Sorangicin A

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**Keywords:** Organocatalysis / Oxygen heterocycles / Michael addition / Configurational switch

Tandem and organocatalytic oxa-Michael reactions of α,β-unsaturated aldehydes were explored for the stereoselective synthesis of structurally complex tetrahydropyrans. The stereoselective synthesis of 2,6-*trans*-tetrahydropyrans, which are thermodynamically unfavorable, was accomplished through a reagent-controlled, organocatalytic oxa-Michael reaction. A temperature-dependent configurational switch allowed the preparation of both 2,3-*trans*-2,6-*trans*- and 2,3-*cis*-2,6-*cis*-tetrahydropyrans from a common substrate. This switch was then used to synthesize the precursors of the C21–C29 and C30–C37 fragments of *ent*-(+)-sorangicin A.

## Introduction

Substituted tetrahydropyrans are important structural motifs found in a wide range of biologically interesting natural products.[1,2] Among substituted tetrahydropyrans, 3-methyl-2,6-disubstituted tetrahydropyrans are one of the most abundant classes in natural products and have attracted considerable interest (Figure 1).[1a,1c,1e,1f] Although an increasing amount of interest has focused on the generation of these structures, it is surprising that the oxa-Michael reaction of α,β-unsaturated aldehydes has rarely been used for the stereoselective synthesis of 3-methyl-2,6-disubstituted tetrahydropyrans.[3,4] In addition, the stereoselective synthesis of 2,6-*trans*-tetrahydropyrans has been a challenge in organic synthesis because of their poor thermodynamic stability.

Recently, we reported the stereoselective synthesis of 2,6-*cis*-tetrahydropyrans through the tandem oxidation/oxa-Michael reaction of α,β-unsaturated aldehydes promoted by the *gem*-disubstituent effect.[5] The reaction required no activation of either the oxygen nucleophiles or the aldehydes. The reaction was applicable to a broad range of substrates and proceeded with excellent stereoselectivity (>20:1 *dr*). We used the oxa-Michael reaction in conjunction with a dithiane coupling reaction to perform the highly stereoselective synthesis of 2,3,6-trisubstituted tetrahydropyrans.[6] We also demonstrated the utility and efficiency of the combination of the oxa-Michael reaction and the dithiane coupling reaction in the stereoselective synthesis of neopeltolide,[5] cyanolide A,[6a] leucascandrolide A,[6b] psymberin,[6c] and SCH 351448.[7]

Intrigued by the excellent efficiency and stereoselectivity of the tandem oxa-Michael reaction of α,β-unsaturated aldehydes in the synthesis of 2,6-*cis*-tetrahydropyrans, we decided to extend this method to the synthesis of 3-methyl-2,6-disubstituted tetrahydropyrans. Herein, we describe our investigation of tandem and organocatalytic oxa-Michael reactions of α,β-unsaturated aldehydes for the stereoselective synthesis of structurally complex tetrahydropyrans and their application to the efficient synthesis of the precursors to the C21–C29 and C30–C37 fragments of *ent*-(+)-sorangicin A.

## Results and Discussion

The tandem oxidation/oxa-Michael reaction required no activation of the substrates and proceeded in a substrate-controlled manner under neutral and mild conditions. Therefore, we proposed that it would be possible to predict the stereochemical outcome of the oxa-Michael reaction through conformational analysis of the transition states (Figure 2).

On the basis that the bulky C2, C3, and C6 substituents of 2,3-*trans*-2,6-*cis*-tetrahydropyran **12** occupy equatorial positions, we expected that **12** could be stereoselectively prepared through the most favorable transition state **11B** in the tandem oxidation/oxa-Michael reaction. We also anticipated that aldehyde (*E*)-**13** should adopt the more favorable chair-like transition state (*E*)-**13B** to stereoselectively provide 2,3-*cis*-2,6-*cis*-tetrahydropyran **14** owing to the severe 1,3-diaxial interaction between the C4 dithiane group and the C6 alkyl group in competing transition state (*E*)-**13A**.

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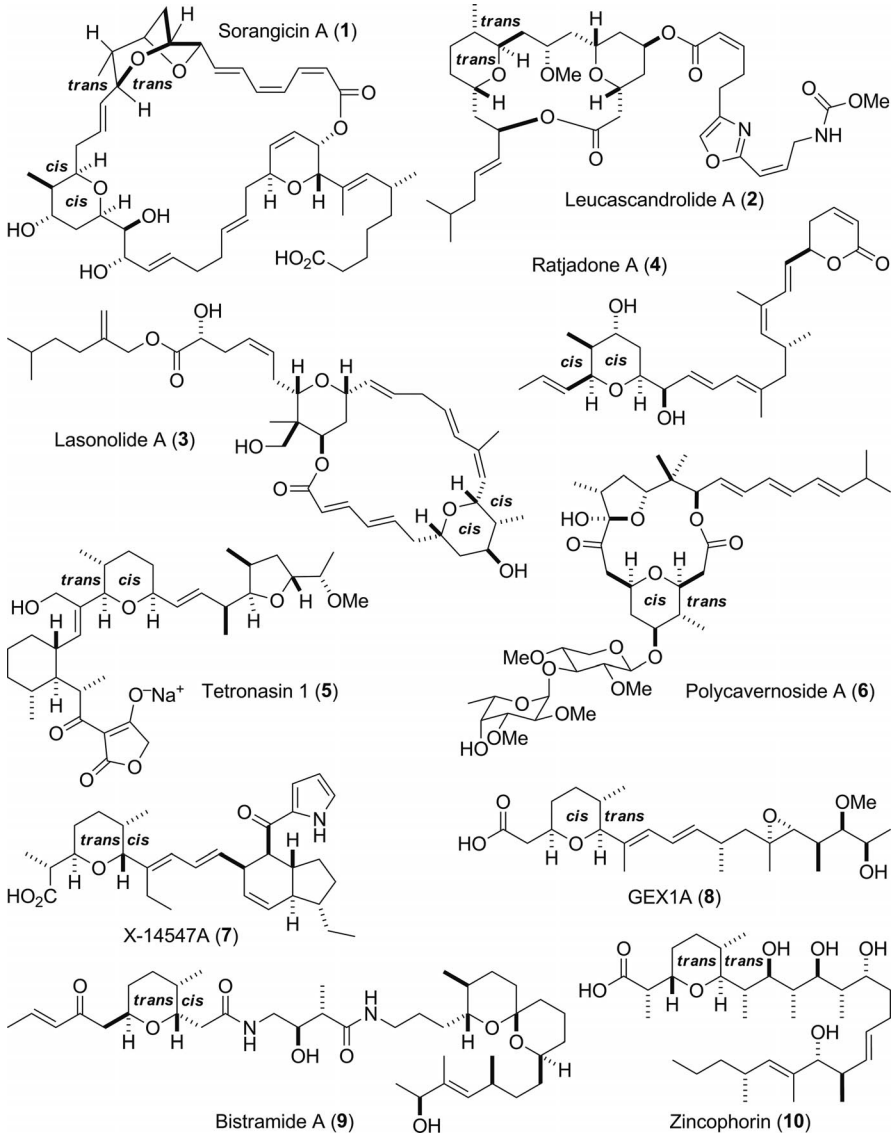



Figure 1. Examples of natural products containing 3-methyl-2,6-disubstituted tetrahydropyrans.

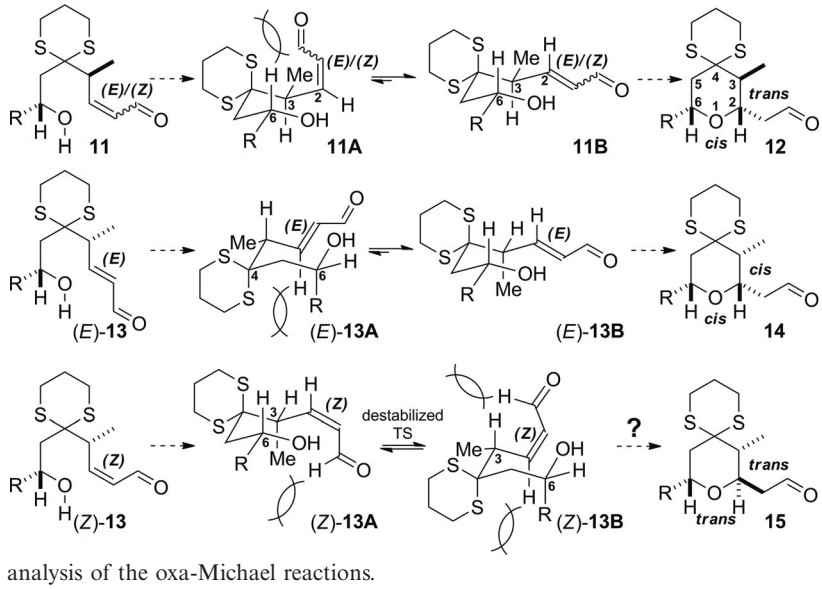
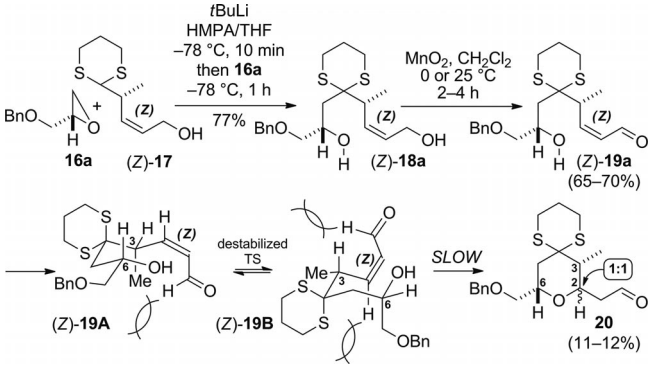



Figure 2. Conformational analysis of the oxa-Michael reactions.

However, the stereoselective synthesis of 2,3-*trans*-2,6-*trans*-tetrahydropyran **15** by using the tandem oxidation/oxa-Michael reaction was expected to be more challenging. A stereochemical mismatch between the C3 methyl group and the C6 alkyl group in (*Z*)-**13A** and (*Z*)-**13B** was expected to hamper the formation of a well-defined transition state in the oxa-Michael step leading to **15**, thus having an impact on the stereoselectivity and reactivity.

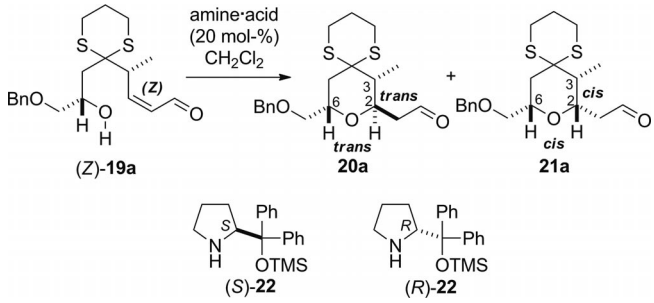
To test the feasibility of the oxa-Michael reaction for the stereoselective synthesis of 2,3-*trans*-2,6-*trans*-tetrahydropyrans, we prepared allyl alcohol (*Z*)-**18a**, by coupling (*Z*)-**17**[6b] and (*S*)-glycidyl benzyl ether (**16a**), and subjected it to the tandem oxidation/oxa-Michael reaction (Scheme 1). As predicted, the tandem reaction of (*Z*)-**18a** provided aldehyde (*Z*)-**19a** as the major product (65–70%) because of repulsive interactions in the transition states. Both starting material and product also decomposed during the prolonged reaction time (72 h).




Scheme 1. Preparation of allyl alcohol (*Z*)-**18a** and attempts towards the synthesis of 2,3-*trans*-2,6-*trans*-tetrahydropyrans through the tandem oxa-Michael reaction.

To overcome the stereochemical mismatch in the transition states and to promote the oxa-Michael step by increasing the reactivity of (*Z*)-**19a**, we converted (*Z*)-**19a** into the corresponding iminium ion by reacting it with a range of amines and acids (Table 1). The iminium activation of (*Z*)-**19a** by treatment with pyrrolidine and BzOH at 25 °C dramatically promoted the oxa-Michael reaction, but afforded undesired 2,3-*cis*-2,6-*cis*-tetrahydropyran **21a** as a single diastereomer (Table 1, Entry 1).[8] Surprisingly, when the reaction was attempted at low temperature (–40 or –78 °C), the stereoselectivity was reversed to provide 2,3-*trans*-2,6-*trans*-tetrahydropyran **20a** as the major diastereomer (3.5–4.1:1 *dr*; Table 1, Entries 2 and 3).[8] Use of piperidine as an alternative amine source further improved the stereoselectivity (7.4:1 *dr*; Table 1, Entry 6). Encouraged by these results, we decided to test chiral organocatalysts to further improve the stereoselectivity of the oxa-Michael reaction.[9,10] When (*Z*)-**19a** was treated with (*S*)-**22**[11] at –40 °C, the organocatalytic oxa-Michael reaction proceeded smoothly to provide **20a** with excellent stereoselectivity and yield (12:1 *dr*, 96%; Table 1, Entry 9). When (*R*)-**22** was employed, the organocatalytic oxa-Michael reaction provided **20a** with no stereoselectivity (Table 1, Entry 10).

Table 1. The organocatalytic oxa-Michael reaction of α,β-unsaturated aldehydes.




| Entry | Amine | Acid | *T* [°C] | Time [h] | Yield [%][a] | *dr*[b] |
|---|---|---|---|---|---|---|
| 1 | pyrrolidine | BzOH | 25 | 1 | 98 | **21a** only |
| 2 | pyrrolidine | BzOH | –40 | 4 | 96 | 3.5:1 |
| 3 | pyrrolidine | BzOH | –78 | 14 | 93 | 4.1:1 |
| 4 | pyrrolidine | HOAc | –40 | 4 | 95 | 3:1 |
| 5 | pyrrolidine | TFA | –40 | 5 | 75 | 2.5:1 |
| 6 | piperidine | BzOH | –40 | 13 | 95 | 7.4:1 |
| 7 | (*S*)-**22** | BzOH | 0 | 3 | 96 | 6:1 |
| 8 | (*S*)-**22** | BzOH | –20 | 5 | 93 | 10:1 |
| 9 | (*S*)-**22** | BzOH | –40 | 14 | 96 | 12:1 |
| 10 | (*R*)-**22** | BzOH | 0 | 3 | 95 | 1:1 |

[a] Combined yield of isolated **20a** and **21a**. [b] The diastereomeric ratio (**20a**/**21a**) was determined by integration of relevant $^1$H NMR spectroscopic signals of the crude product.

Our proposed rationales (Rationale 1 and Rationale 2, Figure 3) for the stereochemical outcome, as a function of reaction temperature observed in the organocatalytic oxa-Michael reaction, are illustrated in Figure 3. Rationale 1 shows that at low temperature (–40 or –78 °C), the iminium ion of (*Z*)-**19a** would adopt conformation **23B** to avoid the severe 1,3-diaxial interaction between the axially oriented C3 methyl group and the C2 iminium diene group to afford 2,3-*trans*-2,6-*trans*-tetrahydropyran **20a**. At 25 °C, (*Z*)-iminium ions **23A** and **23B** readily undergo isomerization to give the more stable (*E*)-iminium ion **23C**, which subsequently cyclizes to give the kinetically and thermodynamically more favorable product 2,3-*cis*-2,6-*cis*-tetrahydropyran **21a**. An alternative explanation (Rationale 2) is that the iminium ion of (*Z*)-**19a** initially forms the kinetically more favorable product **20a** at 25 °C. Compound **20a** could then be converted into the corresponding (*E*)-enal through a retro-Michael reaction to form **21a**. The low reaction temperature would minimize the isomerization of (*Z*)-iminium ions and/or the retro-Michael/isomerization/oxa-Michael reaction of **20a**. When **20a** was subjected to the oxa-Michael reaction conditions (pyrrolidine, BzOH and $CH_2Cl_2$ at 25 °C for 2.5 h), **21a** (96%, >20:1 *dr*) was formed exclusively, suggesting that Rationale 2 is most likely. Because no equilibrium in the retro-Michael reaction was observed for the tandem oxidation/oxa-Michael reaction,[5] the equilibrium between **20a** and **21a** observed in the organocatalytic oxa-Michael reaction was attributed to activation by the iminium ion formation and/or the stereochemical mismatch between the C3 methyl group and the C6 alkyl chain in **20a**.

To the best of our knowledge, this is the first report of a temperature-dependent configurational switch for the synthesis of both 2,3-*trans*-2,6-*trans*- and 2,3-*cis*-2,6-*cis*-tetrahydropyrans from a common substrate by using oxa-Michael reactions.

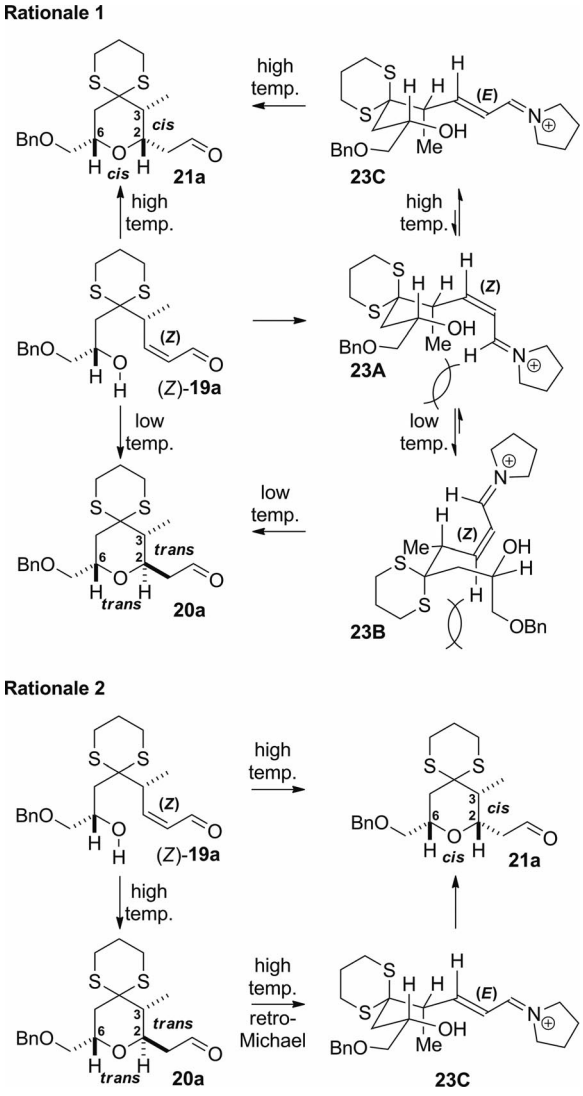
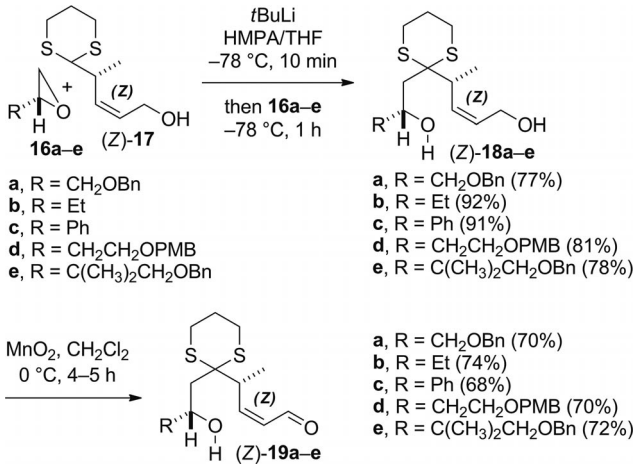



Figure 3. Proposed rationales for the stereochemical outcome of the organocatalytic oxa-Michael reaction.

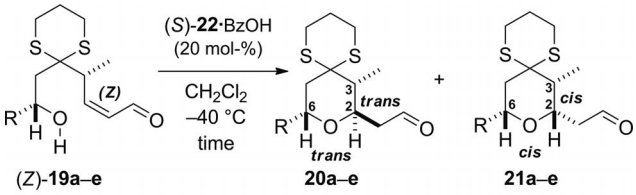
To investigate the substrate scope and stereochemical outcome of the organocatalytic oxa-Michael reaction, we prepared α,β-unsaturated aldehydes (*Z*)-**19a**–**e** with a variety of substituents at the C6 position by coupling (*Z*)-**17** with commercially or readily available chiral epoxides **16a**–**e** (Scheme 2).

Under the standard reaction conditions [(*S*)-**22** and BzOH in $CH_2Cl_2$ at –40 °C], the organocatalytic oxa-Michael reaction of (*Z*)-**19a**–**e** proceeded smoothly to provide the corresponding 2,3-*trans*-2,6-*trans*-tetrahydropyran aldehydes **20a**–**e** with good to excellent stereoselectivities (11–20:1 *dr*; Table 2).




Scheme 2. Preparation of α,β-unsaturated aldehydes (*Z*)-**19a**–**e** for the organocatalytic oxa-Michael reaction.

Table 2. Substrate scope of the organocatalytic oxa-Michael reaction.



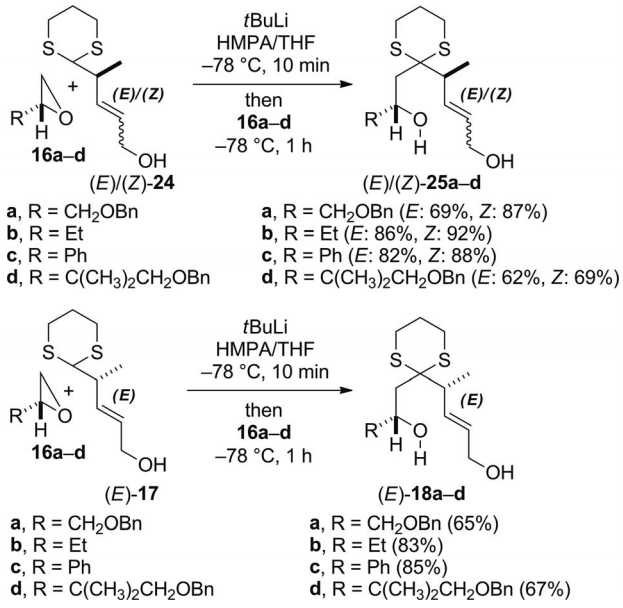

| Entry | Substrate | Time [h] | Yield [%][a] | *dr*[b] |
|---|---|---|---|---|
| 1 | **19a** | 14 | 96 | 12:1 |
| 2 | **19b** | 7 | 97 | 20:1 |
| 3 | **19c** | 8 | 98 | 11:1 |
| 4 | **19d** | 13 | 98 | >20:1 |
| 5 | **19e** | 12 | 95 | 13:1 |

[a] Combined yield of the isolated 2,3-*trans*-2,6-*trans*- and 2,3-*cis*-2,6-*cis*-tetrahydropyrans. [b] The diastereomeric ratio (2,3-*trans*-2,6-*trans*-tetrahydropyran/2,3-*cis*-2,6-*cis*-tetrahydropyran) was determined by integration of the $^1$H NMR spectroscopic signals of the crude product.

As illustrated in Figure 2, conformational analysis suggested that the stereoselective synthesis of 2,3-*trans*-2,6-*cis*-tetrahydropyrans and 2,3-*cis*-2,6-*cis*-tetrahydropyrans through the tandem oxa-Michael reaction should be straightforward. To explore the utility of the tandem oxa-Michael reaction in the stereoselective synthesis of these compounds, we prepared allyl alcohols (*E*)-**25a**–**d**, (*Z*)-**25a**–**d**, and (*E*)-**18a**–**d** by coupling (*E*)-**24**, (*Z*)-**24**, and (*E*)-**17**, respectively, with chiral epoxides **16a**–**d** (Scheme 3).

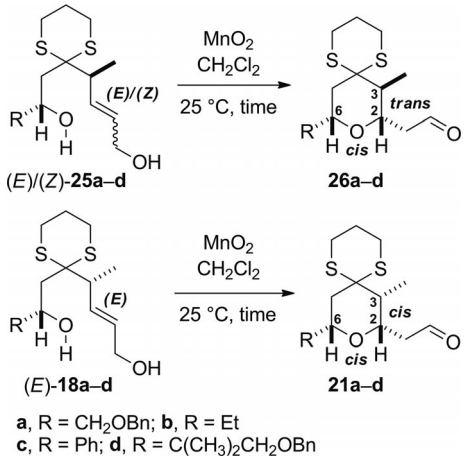
As expected, the tandem oxa-Michael reaction ($MnO_2$ in $CH_2Cl_2$ at 25 °C) of (*E*)- and (*Z*)-**25a**–**d** afforded 2,3-*trans*-2,6-*cis*-tetrahydropyrans **26a**–**d** with excellent stereoselectivities (Table 3, Entries 1–8).[8,12] Under the same reaction conditions, (*E*)-**18a**–**d** gave rise to 2,3-*cis*-2,6-*cis*-tetrahydropyrans **21a**–**d** as single diastereomers (Table 3, Entries 9–12).[8]




Scheme 3. Preparation of allyl alcohols.

Table 3. Synthesis of 2,3-*trans*-2,6-*cis*- and 2,3-*cis*-2,6-*cis*-tetrahydropyrans **26a**–**d** and **21a**–**d** through tandem oxa-Michael reactions.




| Entry | Substrate | Time [h] | Yield [%] | *dr*[a] |
|---|---|---|---|---|
| 1 | (*E*)-**25a** | 12 | 83 | >20:1 |
| 2 | (*E*)-**25b** | 12 | 90 | >20:1 |
| 3 | (*E*)-**25c** | 12 | 83 | >20:1 |
| 4 | (*E*)-**25d** | 12 | 82 | >20:1 |
| 5 | (*Z*)-**25a** | 10 | 84 | >20:1 |
| 6 | (*Z*)-**25b** | 10 | 85 | >20:1 |
| 7 | (*Z*)-**25c** | 10 | 81 | >20:1 |
| 8 | (*Z*)-**25d** | 12 | 88 | >20:1 |
| 9 | (*E*)-**18a** | 10 | 87 | >20:1 |
| 10 | (*E*)-**18b** | 10 | 84 | >20:1 |
| 11 | (*E*)-**18c** | 10 | 85 | >20:1 |
| 12 | (*E*)-**18d** | 12 | 81 | >20:1 |

[a] The diastereomeric ratio was determined by integration of the $^1$H NMR spectroscopic signals of the crude product.

The tandem and organocatalytic oxa-Michael reactions of α,β-unsaturated aldehydes can be broadly applicable to the stereoselective synthesis of structurally complex tetrahydropyrans and natural products. To demonstrate the efficiency of the temperature-dependent configurational switch from a common substrate, we synthesized the precursors to the C21–C29 and C30–C37 fragments of *ent*-(+)-sorangicin A (*ent*-**1**, Figure 4). The marine macrolide (+)-sorangicin A (**1**, Figure 1) was isolated from the myxobacterium *Sorangium cellulosum* by Jansen and co-workers.[13] (+)-Sorangicin A is active against both Gram-positive (MIC = 0.01–0.1 μg/mL) and Gram-negative (MIC = 3–30 μg/mL) bacteria.[14] Reichenbach and co-workers determined that the antibacterial activity of **1** arises from its inhibition of RNA polymerase.[14] Owing to its potent antibiotic activity and architectural complexity, the synthesis of **1** has attracted considerable interest from a number of groups,[15–17] with the first total synthesis reported by Smith and co-workers.[15] We envisioned that both 2,3-*trans*-2,6-*trans*-tetrahydropyran and 2,3-*cis*-2,6-*cis*-tetrahydropyran units embedded in *ent*-**1** could be constructed from a common substrate through the temperature-dependent configurational switch of the organocatalytic oxa-Michael reaction.

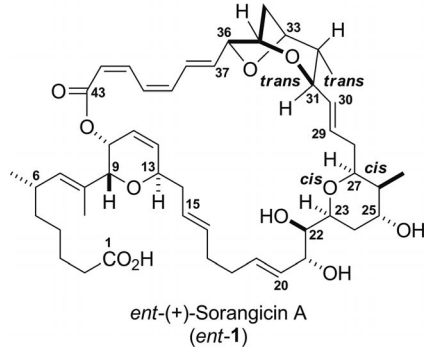
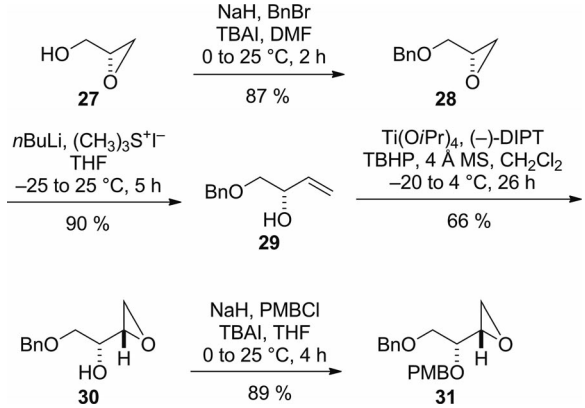



Figure 4. Structure of *ent*-(+)-sorangicin A (*ent*-**1**).

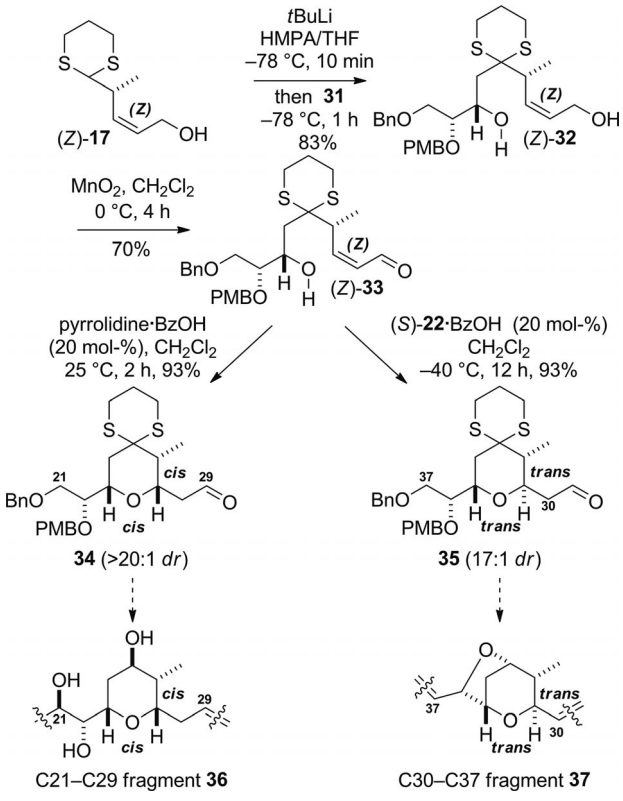
The synthesis of the precursors to the C21–C29 and C30–C37 fragments of *ent*-**1** started with the preparation of chiral epoxide **31** (Scheme 4). Bn protection of commercially available (*R*)-(+)-glycidol (**27**), opening of epoxide **28** by trimethylsulfonium iodide, and Sharpless asymmetric epoxidation of allyl alcohol **29** provided known epoxide **30**.[18] Protection of **30** by using *p*-methoxybenzyl chloride completed the synthesis of chiral epoxide **31**.



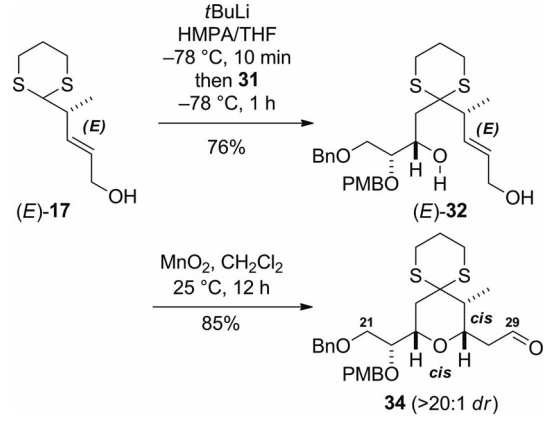

Scheme 4. Preparation of chiral epoxide **31**.

Dithiane coupling of (*Z*)-**17** with **31** followed by $MnO_2$ oxidation of the corresponding allyl alcohol (*Z*)-**32** set the stage for the organocatalytic oxa-Michael reactions (Scheme 5). The organocatalytic oxa-Michael reaction of (*Z*)-**33** at *25 °C* in the presence of pyrrolidine proceeded smoothly to provide 2,3-*cis*-2,6-*cis*-tetrahydropyran **34** as a single diastereomer (>20:1 *dr*).[12] When (*S*)-**22** was used for the oxa-Michael reaction of (*Z*)-**33** at *–40 °C*, 2,3-*trans*-2,6-*trans*-tetrahydropyran **35** was obtained with excellent stereoselectivity (17:1 *dr*). The temperature-dependent configurational switch was successfully used to prepare diastereomeric tetrahydropyrans **34** and **35** from common substrate (*Z*)-**33**.




Scheme 5. Synthesis of the precursors to the C21–C29 and C30–C37 fragments of *ent*-**1** through the organocatalytic oxa-Michael reaction.




Scheme 6. Synthesis of the precursor to the C21–C29 fragment of *ent*-(+)-sorangicin A through a tandem oxidation/oxa-Michael reaction.

In addition, the tandem oxidation/oxa-Michael reaction was effective in the stereoselective synthesis of 2,3-*cis*-2,6-*cis*-tetrahydropyran **34** as a single diastereomer (Scheme 6). Coupling of (*E*)-**17** and **31** provided allyl alcohol (*E*)-**32** in 76% yield. The tandem oxidation/oxa-Michael reaction of (*E*)-**32** ($MnO_2$ in $CH_2Cl_2$ at 25 °C for 12 h) proceeded smoothly to provide **34** with excellent stereoselectivity and yield (>20:1 *dr*, 85%). Compounds **34** and **35** can be further elaborated into C21–C29 fragment **36** and C30–C37 fragment **37** of *ent*-**1**.

## Conclusion

In summary, tandem and organocatalytic oxa-Michael reactions have been used to stereoselectively synthesize structurally complex tetrahydropyrans. In particular, the synthesis of thermodynamically unfavorable 2,6-*trans*-tetrahydropyrans was achieved through a reagent-controlled, organocatalytic oxa-Michael reaction. A temperature-dependent configurational switch allowed the preparation of both 2,3-*trans*-2,6-*trans*- and 2,3-*cis*-2,6-*cis*-tetrahydropyrans from a common substrate, which was applied in the synthesis of the precursors to the C21–C29 and C30–C37 fragments of *ent*-(+)-sorangicin A. We expect that tandem and organocatalytic oxa-Michael reactions will be used for the stereoselective synthesis of a diverse set of tetrahydropyrans and be applied to the synthesis of complex natural products with interesting biological activities.

## Experimental Section

**General Methods:** All reactions were conducted in oven-dried glassware under nitrogen. All commercial chemical reagents were used as supplied. Anhydrous tetrahydrofuran (THF) was distilled from sodium/benzophenone. Analytical thin layer chromatography (TLC) was performed on $SiO_2$ (60 Å) with florescent indication (Whatman). Visualization was accomplished by UV irradiation at 254 nm and/or by staining with *para*-anisaldehyde solution. Flash column chromatography was performed by using silica gel 60 (particle size 4063 μm, 230400 mesh). $^1H$ NMR, $^{13}C$ NMR, and 2D NMR (COSY, NOESY) spectra were recorded with a Varian 400 (400 MHz) and a Bruker 500 (500 MHz) spectometer in $CDCl_3$ by using the signal of residual $CHCl_3$ as an internal standard. All NMR $\delta$ values are given in ppm, and all *J* values are in Hz. Electrospray ionization (ESI) mass spectra (MS) were recorded with an Agilent 1100 series (LC/MSD trap) spectrometer and were performed to obtain the molecular masses of the compounds. Infrared (IR) absorption spectra were determined with a Thermo-Fisher (Nicolet 6700) spectrometer. Optical rotation values were measured with a Rudolph Research Analytical (A21102, API/1W) polarimeter.

**Typical Procedure for the Organocatalytic Oxa-Michael Reaction:** To a cooled (–40 °C) solution of aldehyde (*Z*)-**19a** (28.8 mg, 0.079 mmol) in $CH_2Cl_2$ (0.039 M, 2.0 mL) was added dropwise a mixture of (*S*)-(–)-α,α-diphenyl-2-pyrrolidinemethanol trimethylsilyl ether (5.1 mg, 0.016 mmol) and BzOH (2.0 mg, 0.016 mmol)

in $CH_2Cl_2$ (0.5 mL). After stirring at –40 °C for 14 h, the reaction mixture was diluted with hexanes (25.0 mL), filtered through a short pad of silica gel (hexanes/EtOAc, 3:1), and concentrated in vacuo. The residue was purified by column chromatography (silica gel; hexanes/EtOAc, 2:1) to afford 2,3-*trans*-2,6-*trans*-tetrahydropyran **20a** (25.9 mg, 90%) and 2,3-*cis*-2,6-*cis*-tetrahydropyran **21a** (2.1 mg, 7%) as colorless oils. Data for **20a**: $[\alpha]_D^{25}$ = +16.0 (*c* = 0.92, $CHCl_3$). $^1$H NMR (500 MHz, $CDCl_3$): $\delta$ = 9.75 (dd, *J* = 2.0, 2.0 Hz, 1 H), 7.26–7.37 (m, 5 H), 4.54 (s, 2 H), 4.25 (ddd, *J* = 7.0, 7.0, 7.0 Hz, 1 H), 4.15 (dddd, *J* = 5.5, 5.5, 5.5, 5.5 Hz, 1 H), 3.80 (dd, *J* = 6.0, 1.5 Hz, 2 H), 3.08 (ddd, *J* = 14.5, 11.5, 3.0 Hz, 1 H), 2.96 (ddd, *J* = 14.5, 11.5, 3.0 Hz, 1 H), 2.65–2.75 (m, 5 H), 2.26 (dd, *J* = 14.5, 5.5 Hz, 1 H), 2.00–2.07 (m, 1 H), 1.94 (dddd, *J* = 7.0, 7.0, 7.0, 7.0 Hz, 1 H), 1.79–1.89 (m, 1 H), 1.21 (d, *J* = 7.0 Hz, 3 H) ppm. $^{13}$C NMR (125 MHz, $CDCl_3$): $\delta$ = 201.4, 138.1, 128.3, 127.6, 73.3, 70.55, 70.37, 69.6, 52.3, 47.5, 43.2, 36.5, 26.1, 25.7, 25.2, 13.9 ppm. IR (neat): $\tilde{\nu}$ = 1722, 1452, 1277, 1097, 906, 738, 698 cm$^{-1}$. HRMS (ESI): calcd. for $C_{19}H_{26}O_3S_2$ [M + H]$^+$ 367.1396; found 367.1396. Data for **21a**: $[\alpha]_D^{25}$ = –26.9 (*c* = 1.07, $CHCl_3$). $^1$H NMR (500 MHz, $CDCl_3$): $\delta$ = 9.77 (dd, *J* = 2.0, 2.0 Hz, 1 H), 7.24–7.36 (m, 5 H), 4.84 (ddd, *J* = 9.5, 4.5, 2.0 Hz, 1 H), 4.53 (AB, $\Delta\upsilon$ = 16.5, $J_{AB}$ = 11.5 Hz, 2 H), 4.06–4.12 (m, 1 H), 3.48 (dd, *J* = 10.5, 5.5 Hz, 1 H), 3.42 (dd, *J* = 10.5, 4.5 Hz, 1 H), 2.66–2.90 (m, 5 H), 2.34 (ddd, *J* = 17.0, 4.5, 2.0 Hz, 1 H), 2.09 (ddd, *J* = 7.5, 7.5, 7.5 Hz, 1 H), 1.90–2.02 (m, 3 H), 1.85 (dd, *J* = 13.5, 11.5 Hz, 1 H), 1.11 (d, *J* = 7.5 Hz, 3 H) ppm. $^{13}$C NMR (125 MHz, $CDCl_3$): $\delta$ = 201.0, 138.1, 128.3, 127.6, 73.3, 72.59, 72.56, 70.1, 53.3, 47.4, 38.3, 34.6, 26.0, 25.4, 25.2, 8.9 ppm. IR (neat): $\tilde{\nu}$ = 1722, 1453, 1376, 1108, 1026, 738, 698 cm$^{-1}$. HRMS (ESI): calcd. for $C_{19}H_{26}O_3S_2$ [M + H]$^+$ 367.1393; found 367.1396.

**Typical Procedure for the Tandem Oxidation/Oxa-Michael Reaction:** To a solution of diol (*E*)-**25a** (15.5 mg, 0.042 mmol) in $CH_2Cl_2$ (0.021 M, 2.0 mL) was added $MnO_2$ (18.3 mg, 0.21 mmol). The resulting mixture was stirred for 1 h at 25 °C. An addition of $MnO_2$ (18.3 mg, 0.21 mmol) was repeated three times every 1 h. After stirring for an additional 6 h, the reaction mixture was filtered through a pad of Celite and concentrated in vacuo. The residue was purified by column chromatography (silica gel; hexanes/EtOAc, 2:1) to afford 2,3-*trans*-2,6-*cis*-tetrahydropyran **26a** (12.8 mg, 83%) as a colorless oil. $[\alpha]_D^{25}$ = +16.4 (*c* = 0.17, $CHCl_3$). $^1$H NMR (500 MHz, $CDCl_3$): $\delta$ = 9.78 (dd, *J* = 3.5, 1.5 Hz, 1 H), 7.26–7.40 (m, 5 H), 4.56 (s, 2 H), 4.09–4.15 (m, 2 H), 3.52 (dd, *J* = 10.0, 5.0 Hz, 1 H), 3.47 (dd, *J* = 10.5, 5.0 Hz, 1 H), 3.14 (ddd, *J* = 14.5, 12.5, 2.5 Hz, 1 H), 2.91 (ddd, *J* = 14.5, 12.0, 2.5 Hz, 1 H), 2.76 (dd, *J* = 14.0, 1.5 Hz, 1 H), 2.62–2.69 (m, 2 H), 2.58 (ddd, *J* = 16.0, 4.0, 2.0 Hz, 1 H), 2.44 (ddd, *J* = 15.5, 9.0, 3.5 Hz, 1 H), 2.05–2.12 (m, 1 H), 1.77–1.88 (m, 2 H), 1.69–1.76 (m, 1 H), 1.16 (d, *J* = 7.0 Hz, 3 H) ppm. $^{13}$C NMR (100 MHz, $CDCl_3$): $\delta$ = 201.6, 138.2, 128.4, 127.7, 73.4, 73.1, 72.8, 72.5, 54.3, 47.4, 45.5, 39.9, 25.68, 25.55, 25.0, 12.2 ppm. IR (neat): $\tilde{\nu}$ = 1722, 1452, 1380, 1054, 908, 736, 698 cm$^{-1}$. HRMS (ESI): calcd. for $C_{19}H_{26}O_3S_2$ [M + H]$^+$ 367.1392; found 367.1396.

**Supporting Information** (see footnote on the first page of this article): Complete characterization data and copies of the $^1$H and $^{13}$C NMR spectra.

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