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Stereoselective Synthesis of 2,6-*trans*-Tetrahydropyran via Primary Diamine-Catalyzed Oxa-Conjugate Addition Reaction of α,β-Unsaturated Ketone: Total Synthesis of Psymberin

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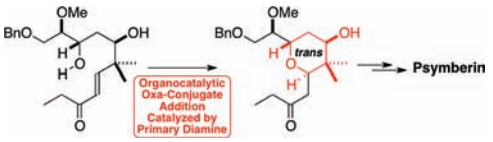
ABSTRACT



The total synthesis of psymberin was achieved employing a readily available chiral epoxide to prepare two of the three subunits in the natural product. The key reaction was a highly stereoselective organocatalytic oxa-conjugate addition reaction of α,β-unsaturated ketone catalyzed by primary diamine for the synthesis of the 2,6-*trans*-tetrahydropyran embedded in psymberin.

The marine cytotoxin psymberin (**1**, Scheme 1) is a potent inhibitor of cancer cell proliferation[1] and has attracted considerable interest from a number of synthetic groups.[2−4] It possesses the psymberic acid side chain, a 2,6-*trans*-3,3-dimethyl tetrahydropyran-4-ol, and a dihydroisocoumarin. One of the synthetic challenges it presents is the stereoselective formation of the 2,6-*trans*-tetrahydropyran subunit. Due to their poor thermodynamic stability, the stereoselective synthesis of 2,6-*trans*-tetrahydropyrans remains a great challenge.[5,6] Displacement of acetate with TMSCN,[2a,3c] configuration-dependent spirodiepoxide opening,[2b] $PhI(OAc)_2$-mediated cyclization,[2c] intramolecular cylization of epoxy alcohols,[2d,f] addition of enolsilane to oxocarbenium ion,[2e] and conjugate addition of vinylmagnesium bromide to dihydropyranone[3f] have been utilized for the synthesis of the 2,6-*trans*-tetrahydropyran in the natural product. Even though the intramolecular

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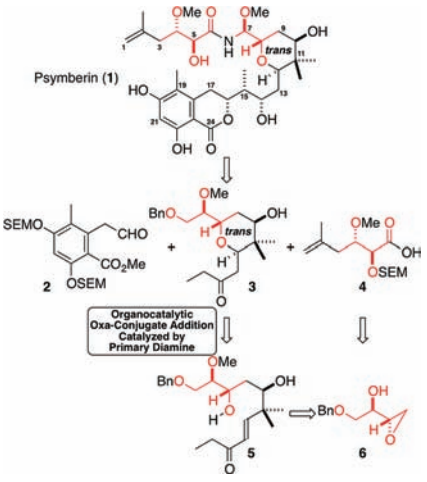
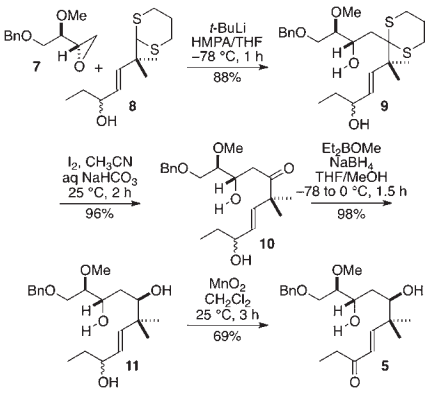
Scheme 1. Retrosynthetic Plan for Psymberin (**1**)



conjugate addition of an oxygen nucleophile to α,β-unsaturated carbonyl compounds (oxa-conjugate addition reaction) is a direct and efficient way to tetrahydropyrans, the oxa-conjugate addition reaction has never been used for the synthesis of **1**.

With an interest in facilitating access to biologically important natural products with tetrahydropyrans,[7] we designed our retrosynthetic plan for **1** relying on the oxa-conjugate addition reaction of α,β-unsaturated ketone **5** catalyzed by primary diamine for the stereoselective synthesis of 2,6-*trans*-3,3-dimethyl tetrahydropyran **3** embedded in **1** (Scheme 1). Because of our previous report on the stereoselective synthesis of 2,6-*cis*-3,3-dimethyl tetrahydropyrans through the tandem oxidation/oxa-Michael reaction of α,β-unsaturated aldehyde,[7d] we envisioned

Scheme 2. Synthesis of Hydroxy Ketone **5**



that it would be challenging to stereoselectively synthesize 2,6-*trans*-3,3-dimethyl tetrahydropyran **3** in a *substrate-controlled manner*. Instead, we decided to explore the organocatalytic oxa-conjugate addition reaction to prepare **3** in a *reagent-controlled manner*. We anticipated that the key intermediates **3** and **4** could be derived from the common chiral epoxide **6**.

The synthesis of psymberin (**1**) started with the preparation of hydroxy ketone **5** (Scheme 2). Coupling[7b,8] of allyl alcohol **8**[9,10] (8 steps from the commercially available 2,2-dimethyl-1,3-propanediol) with the readily available chiral epoxide **7**[10,11] (3 steps from the commercially available (*S*)-(+)-glycidyl benzyl ether) provided **9**. Hydrolysis of the dithiane group of **9**, stereoselective reduction to 1,3-*syn* diol **11** (dr > 20:1),[12] and MnO_2-oxidation of the secondary alcohol **11** set the stage for the key organocatalytic oxa-conjugate addition reaction.

Due to the steric congestion of ketones in iminium formation, we attempted the oxa-conjugate addition reaction catalyzed by primary amine (Table 1).[13–15] The organocatalytic oxa-conjugate addition reaction of **5** in the presence of (1*R*,2*R*)-1,2-diphenylethane-1,2-diamine (**A**)[16] and TFA smoothly proceeded but afforded the undesired 2,6-*cis*-3,3-dimethyl tetrahydropyran **12** as a single diastereomer (entry 1). When HOAc was used in the reaction as

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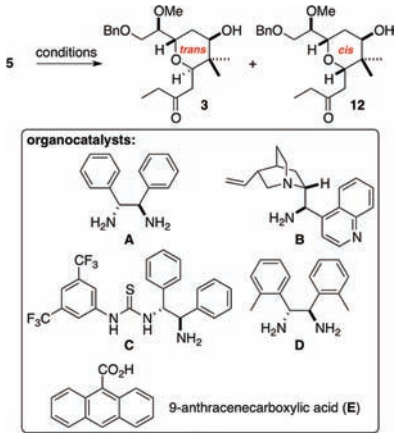
Table 1. Synthesis of 2,6-*trans*-3,3-Dimethyl Tetrahydropyran **3** through the Organocatalytic Oxa-Conjugate Addition Reaction



entry	catalyst (equiv)	acid (equiv)	solvent	temp time	yield (%)[a]	dr[b]
1	**A** (0.4)	TFA (10)	toluene	0 °C 16 h	90	**12** only
2	**A** (0.4)	HOAc (10)	toluene	0 °C 17 h	80	3:1
3	**A** (0.2)	HOAc (10)	toluene	0 °C 46 h	89	3:1
4	**A** (0.4)	HOAc (1)	toluene	0 °C 24 h	93	3:1
5	**B** (0.4)	HOAc (0.8)	toluene	25 °C 44 h	68	1:2
6	**C** (0.4)	HOAc (5)	toluene	0 °C 72 h	79	1:3
7	**A** (0.4)	(1*S*)-10-CSA (1)	toluene	0 °C 14 h	99	**12** only
8	**A** (0.4)	4-pentenoic acid (10)	toluene	0 °C 18 h	95	3.5:1
9	**A** (0.4)	palmitic acid (1)	toluene	0 °C 46 h	94	3:1
10	**A** (0.4)	benzoic acid (1)	toluene	0 °C 16 h	87	2:1
11	**A** (0.4)	1-naphthoic acid (1)	toluene	0 °C 47 h	89	3:1
12	**A** (0.4)	**E** (1)	toluene	0 °C 46 h	92	6:1
13	**A** (0.4)	**E** (1)	EtOAc	0 °C 48 h	92	10:1
14	**D** (0.4)	**E** (1)	EtOAc	0 °C 48 h	78	10:1
15	none	**E** (1)	EtOAc	0 °C 48 h	NR[c]	NA[d]

[a] Combined yield of the isolated **3** and **12**. [b] The diastereomeric ratio (**3**:**12**) was determined by integration of the ^{1}H NMR of the crude product. [c] No reaction. [d] Not applicable.

an alternative acid source, the stereoselectivity was reversed to provide 2,6-*trans*-3,3-dimethyl tetrahydropyran **3** as the major diastereomer (dr = 3:1, entries 2−4). Other primary amines such as 9-amino-9-deoxy-*epi*-cinchonine (**B**)[17] or thiourea (**C**)[18] gave **12** as the major diastereomer (entries 5 and 6). These results implied that the acid used in the organocatalytic oxa-conjugate addition reaction might have

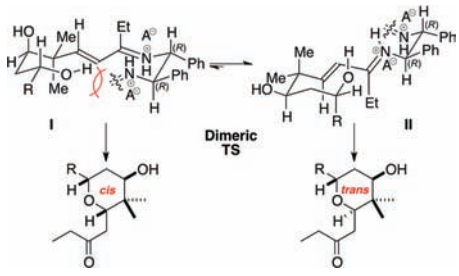


Figure 1. Proposed transition states for the oxa-conjugate addition reaction catalyzed by (1*R*,2*R*)-1,2-diphenylethane-1,2-diamine (A = acid).

a dramatic effect on the stereochemical outcome of the reaction and encouraged us to test various acids to further improve the stereoselectivity of the organocatalytic oxa-conjugate addition reaction. The use of a strong acid such as (1*S*)-10-camphorsulfonic acid (CSA) provided **12** as a single diastereomer (entry 7), suggesting that oxa-conjugate addition reaction might proceed via an acid-catalysis mechanism. Aliphatic acids did not change the stereoselectivity (entries 8 and 9). Finally, when **5** was treated with the combination of **A** and 9-anthracenecarboxylic acid (**E**) in EtOAc, the organocatalytic oxa-conjugate addition reaction proceeded smoothly to provide **3** with high stereoselectivity and yield (dr = 10:1, 92%, entry 13).

Our proposed rationale for the stereochemical outcome as a function of the steric bulkiness of acid is that the use of acid with steric bulkiness enhances the steric repulsions in the less favorable dimeric conformer **I** and increases the population of conformer **II** (Figure 1).[16a,19] Even though the organocatalytic conjugate addition of a carbon nucleophile to α,β-unsaturated ketones has been explored for a direct and efficient way to form C−C bonds, to the

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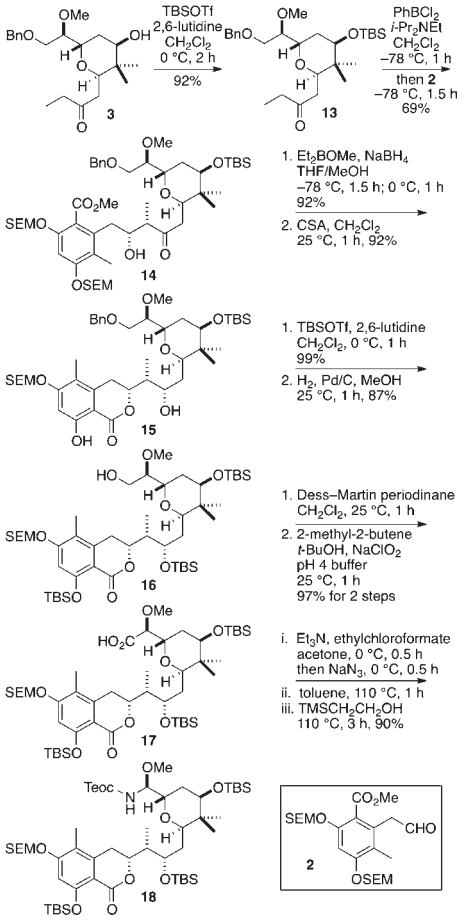
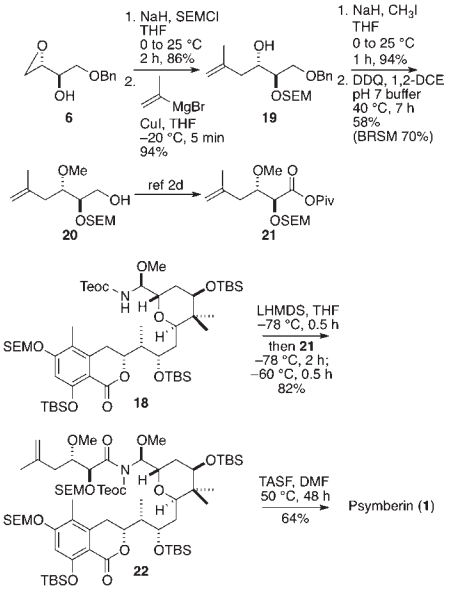
Scheme 3. Aldol Coupling of 2,6-*trans*-Tetrahydropyran **3** and Dihydroisocoumarin **2**



Scheme 4. Synthesis of Pivalate Mixed Anhydride of Psymberic Acid **21** and Completion of the Synthesis of Psymberin (**1**)



best of our knowledge, this is the first report for the organocatalytic oxa-conjugate addition reaction of an alcohol nucleophile to α,β-unsaturated ketones promoted by primary diamine.[20] It would be an effective way to construct β-hydroxy carbonyl compounds.

With the key 2,6-*trans*-3,3-dimethyl tetrahydropyran **3** in hand, we next examined the coupling of 2,6-*trans*-3,3-dimethyl tetrahydropyran **3** and dihydroisocoumarin **2**[2d,3c,21] through the 1,2-*syn*-aldol reaction (Scheme 3). TBS-protection of **3** followed by the aldol addition of **13** to **2** ($PhBCl_2$, *i*-Pr_2NEt, CH_2Cl_2)[2a,d,f] provided the desired β-hydroxy ketone **14** as a single diastereomer. 1,3-*syn*-Reduction (dr = 6:1)[2a,f] followed by lactonization under acidic conditions afforded **15** with loss of the C22 SEM group. TBS-protection, Bn-deprotection, and oxidation provided the corresponding carboxylic acid **17**. Curtius rearrangement following the procedure previously reported by Smith and co-workers smoothly proceeded to give hemiaminal **18**.[2d]

The pivalate mixed anhydride of psymeric acid **21** was prepared from the common epoxide **6** (Scheme 4). SEM-protection, addition of isopropenylmagnesium bromide, methylation, and Bn-deprotection proceeded smoothly to provide **20**. Oxidation to carboxylic acid and formation of pivalate mixed anhydride proceeded smoothly to afford **21**.[2d]

Coupling of **18** with **21** followed by exhaustive deprotection of the silyl protecting groups completed the synthesis of **1**.[2d]

In summary, the total synthesis of psymberin (**1**) was accomplished in 24 steps (in the longest sequence from 2,2-dimethyl-1,3-propanediol) enlisting the oxa-conjugate addition reaction. The organocatalytic oxa-conjugate addition reaction of α,β-unsaturated ketone **5** promoted by primary diamine was explored for the stereoselective synthesis of 2,6-*trans*-3,3-dimethyl tetrahydropyran **3**. It was demonstrated that the stereochemical outcome of the reaction depends on the steric bulkiness of acid used as an additive. It is noteworthy that two of the three subunits in **1** were derived from the readily avaible chiral epoxide **6**.

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Supporting Information Available. General experimental procedures including spectroscopic and analytical data along with copies of ^1H and ^{13}C NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

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