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Enantioselective Synthesis of 2,6-*cis*-Disubstituted Tetrahydropyrans via a Tandem Catalytic Asymmetric Hydrogenation/Oxa-Michael Cyclization: An Efficient Approach to (−)-Centrolobine

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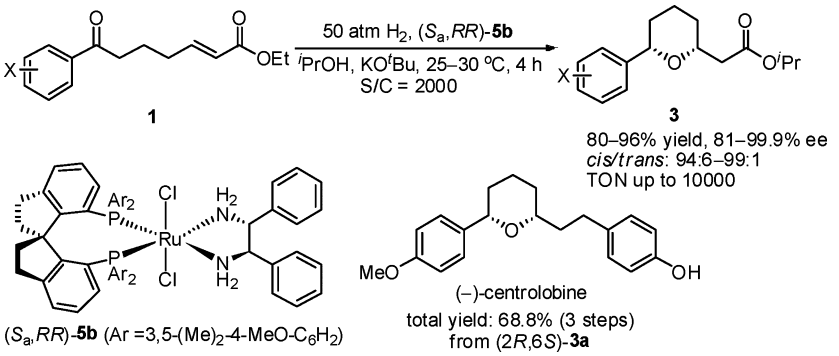
ABSTRACT



A highly efficient one-pot process via a tandem reaction of catalytic asymmetric hydrogenation and oxa-Michael cyclization for the synthesis of 2,6-*cis*-disubstituted tetrahydropyrans has been developed (ee up to 99.9%, *cis*/*trans*-selectivity up to 99:1). This method provides a concise route to (−)-centrolobine (68.8% yield, three steps).

Chiral 2,6-*cis*-disubstituted tetrahydropyrans are common structural motifs that can be found in numerous natural products with significant biological activity (Figure 1). For example, (−)-centrolobine, isolated from the heartwood of *Centrolobium robustum* and the stem of *Brosimum potabile*,[1] exhibits anti-inflammatory, antibacterial, and antileishmanial activities.[2] The macrocyclic lactone (−)-exiguolide, isolated from the marine sponge *Geodia exigua*,[3] inhibits the fertilization of sea urchin gametes.[4] (+)-SCH 351448, discovered in the organic extract of the fermentation broth of a *Micromonospora* microorganism,[5] is a novel activator of the low-density lipoprotein receptor promoter. The synthesis of these and other similar natural products requires the enantioselective construction of one or more chiral 2,6-*cis*-disubstituted tetrahydropyran units, which is a challenging task.

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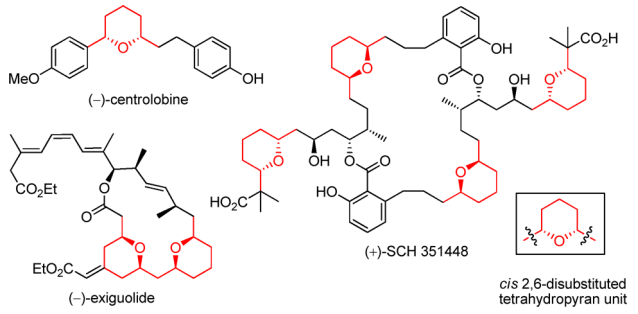
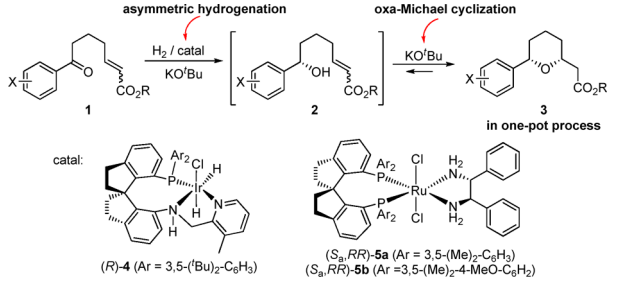


Figure 1. Selected bioactive natural products containing one or more chiral *cis*-2,6-disubstituted tetrahydropyran units.

Over the past decades, considerable effort has been devoted to the development of efficient methods for constructing chiral 2,6-*cis*-disubstituted tetrahydropyran units for the synthesis of natural products containing a tetrahydropyran motif.[6] The intramolecular oxa-Michael addition, also referred to as oxa-Michael cyclization, is one such method.[7] However, most reported syntheses of optically pure 2,6-*cis*-disubstituted tetrahydropyrans using this method required preinstalled chiral centers on the oxyanion groups.[8] Although the transition-metal-catalyzed asymmetric hydrogenation of ketones is a highly efficient and straightforward method for the preparation of chiral alcohols,[9] the enantioselective synthesis of chiral 2,6-*cis*-disubstituted tetrahydropyrans via consecutive asymmetric ketone hydrogenation and oxa-Michael cyclization has not been reported in the literature, to the best of our knowledge.

Recently, we found that chiral iridium[10] and ruthenium complexes[11] bearing a chiral spiro ligand efficiently catalyze the hydrogenation of a wide range of ketones to the corresponding chiral alcohols with excellent enantioselectivities. In these reactions, a strong base such as KO^{t}Bu is required for activating the catalysts. Because KO^{t}Bu is also a good promoter for the oxa-Michael cyclization,[8e−k] we envisioned the asymmetric hydrogenation of arylketones **1** bearing an α,β-unsaturated ester group catalyzed by the Ir-SpiroPAP catalyst (**4**)[10c,d] or $RuCl_2$-(SDPs)(DPEN) (**5**)[11] to generate chiral hydroxy enoates **2**, which would undergo an oxa-Michael cyclization to afford chiral 2,6-*cis*-disubstituted tetrahydropyrans **3** in a one-pot process (Scheme 1). In this communication, we report our initial studies on the development of a tandem process involving asymmetric ketone hydrogenation and base-promoted oxa-Michael cyclization to produce chiral 2,6-*cis*-disubstituted tetrahydropyrans in high yields with excellent enantioselectivities (up to 99.9% ee) and *cis*-selectivities (*cis*/*trans* ratios up to 99:1). This highly efficient one-pot process was used for the enantioselective total synthesis of (−)-centrolobine.

Scheme 1. Tandem Process for the Construction of Chiral 2,6-*cis*-Disubstituted Tetrahydropyrans



Acrylate-containing arylketones **1** were easily prepared from δ-valerolactone in three steps, including a Horner−Wadsworth−Emmons reaction,[12] in good to high yields (see Supporting Information). We then used (*E*)-ethyl 7-(4-methoxyl)-7-oxohept-2-enoate (**1a**) as a substrate to optimize the conditions for the hydrogenation/cyclization reaction (Table 1). When the reaction was performed with iridium catalyst (*R*)-**4** in EtOH under 10 atm of H_2 at room temperature for 4 h in the presence of KO^{t}Bu, the desired 2,6-disubstituted tetrahydropyran **3a** (ethyl ester) was obtained in good yield (85%) and excellent enantioselectivity (95% ee) with high *cis*-selectivity (*cis*/*trans* = 96:4, entry 1),[13] albeit accompanied by an approximately 8% yield of the undesired overhydrogenated product ethyl 7-hydroxy-7-(4-methoxyphenyl)-heptanoate. When $RuCl_2$-(SDPs)(DPEN) ((*S*$_a$,*RR*)-**5a**) was used as the catalyst (KO^{t}Bu, 50 atm of H_2, ^{i}PrOH, room temperature), **3a** (isopropyl ester) was obtained in 96% yield and 98% ee (*cis*/*trans* = 96:4, entry 2), and none of the overhydrogenated

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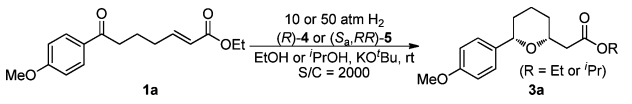
(13) The *cis*/*trans* selectivity of the reaction was very low (*ca.* 63:37) when the hydrogenation was completed; however, it increased to 96:4 after removal of the solvent slowly (6−10 h) in vacuo at room temperature.

byproduct was observed. An even better result was achieved with catalyst (S_a,*RR*)-**5b**, which gave **3a** (isopropyl ester) in 96% yield with up to 99% ee (*cis*/*trans* = 97:3, entry 3). We also studied the effect of KO^{t}Bu concentration on the reaction and found that decreasing the concentration from 0.06 to 0.02 M diminished the *cis*-selectivity of the reaction (*cis*/*trans* = 91:9, entry 5). Catalyst (S_a,*RR*)-**5b** was so active that the reaction could be performed at a catalyst loading as low as 0.01 mol % (S/C = 10 000, entry 6).

Table 1. Optimization of Reaction Conditions for the Synthesis of **3a**[a]



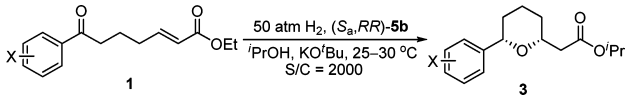
entry	cat.	$P(H_2)$ (atm)	[KO^{t}Bu]	*cis*/*trans*[b]	yield (%)[c]	ee (%)[d]
1	(*R*)-**4**	10	0.06	96:4	85	95
2	(S_a,*RR*)-**5a**	50	0.06	96:4	96	98
3	(S_a,*RR*)-**5b**	50	0.06	97:3	96	99
4	(S_a,*RR*)-**5b**	50	0.04	94:6	95	99
5	(S_a,*RR*)-**5b**	50	0.02	91:9	94	99
6[e]	(S_a,*RR*)-**5b**	50	0.06	96:4	95	98

[a] Reaction conditions: 4.0 mmol scale, [substrate] = 0.4 M, 0.05 mol % catalyst, [KO^{t}Bu] = 0.02−0.06 M, solvent volume = 10.0 mL, room temperature (25−30 °C), and the hydrogenations were completed within 4 h. **3a** was obtained as an ethyl ester for entry 1 and as an isopropyl ester for entries 2−6. [b] The *cis*/*trans* selectivities were obtained by removing solvent slowly in vacuo at room temperature and determined by GC. [c] Total isolated yield of *cis*- and *trans*-isomers. [d] Determined by HPLC using chiral column. According to our previous study (ref 11a) the absolute configuration of the product was assigned as (2*R*,6*S*), which was reaffirmed by converting the product to (−)-centrolobine and comparing the optical rotation with literature data. [e] S/C = 10 000.

We then used the optimal reaction conditions to evaluate several ethyl 7-aryl-7-oxohept-2-enoates **1** (Table 2). The configuration of the double bond of the acrylate group of the substrates had a negligible effect on the asymmetric hydrogenation/oxa-Michael cyclization; the reactions of (*E*)-**1a** and (*Z*)-**1a**, as well as (*Z*/*E*)-**1a**, afforded **3a** in nearly the same yields and selectivities (entries 1−3). Generally, the electronic properties of the substituents on the phenyl ring of the substrates had little effect on either the enantioselectivity or the *cis*-selectivity. However, substrates with an electron-withdrawing substituent such as chloride (**1d**) gave lower yields (79%, entry 6), and a substrate with an *ortho*-methoxy group (**1h**) showed a lower yield (80%) and a lower enantioselectivity (81% ee, entry 10). However, we were gratified to find that the yields of **3d** (87%, entry 6) and **3h** (90%, entry 10), and the enantiomeric excess of **3h** (99.9% ee, entry 10), were significantly improved when (*R*)-**4** was used instead of (S_a,*RR*)-**5b**.

Acrylate-containing arylketones **6** and **8**, which are potential starting materials for the construction of chiral disubstituted oxa-cyclic ether structures such as tetrahydrofurans and isochromans, were also evaluated as substrates

Table 2. Enantioselective Synthesis of *cis*-2,6-Disubstituted Tetrahydropyrans **3**[a]



entry	X	**3**	*cis*/*trans*[b]	yield (%)[c]	ee (%)[d]
1	4-MeO(*E*)	**3a**	97:3	96	99
2	4-MeO(Z)	**3a**	96:4	94	98
3	4-MeO(*Z*,*E*)	**3a**	96:4	95	99
4	H(*E*)	**3b**	96:4	90	99.3
5	4-Me(*E*)	**3c**	97:3	90	99
6[e]	4-Cl(*E*)	**3d**	98:2(99:1)	79(87)	99.7(98)
7	3,4-(MeO)$_2$(*E*)	**3e**	94:6	93	99.5
8	3-MeO(*E*)	**3f**	96:4	86	99.1
9	3-Me(*E*)	**3g**	97:3	85	99.3
10[e]	2-MeO(*E*)	**3h**	98:2(98:2)	80(90)	81(99.9)

[a] Reaction conditions are the same as those in Table 1, entry 3. [b] The *cis*/*trans* selectivities were determined by GC after removing solvent slowly in vacuo at room temperature. [c] Total isolated yield of *cis*- and *trans*-isomers. [d] Determined by HPLC using chiral column. [e] The data in parentheses were obtained with catalyst (*R*)-**4** in ethanol, and the products were ethyl ester.

for the hydrogenation/oxa-Michael cyclization (Scheme 2). Iridium catalyst (*R*)-**4** had higher activity and gave better results than ruthenium catalyst (S_a,*RR*)-**5b** in the reactions of **6** and **8**. Hydrogenation of **6a** and **8a** with (*R*)-**4** afforded oxa-cyclic ether products **7a** and **9a** in good yields (81% and 92%, respectively) and high enantioselectivities (99.9% and 95% ee, respectively), albeit with a 1:1 *cis*/*trans* ratio. Although the hydrogenation of **8b** provided isochroman **9b** with excellent enantioselectivity (99% ee), the yield (60%) and *cis*-selectivity (*cis*/*trans* = 74:26) were only moderate. The moderate yield was attributed mainly to the side reactions of **8b** in the presence of strong base KO^{t}Bu (see Supporting Information). Because α,β-unsaturated ketoester **6b** was particularly sensitive to base and the corresponding ketone-reduction product formed a seven-membered ring with difficulty, no desired oxa-cyclic ether product was obtained. Instead, hydrogenation of

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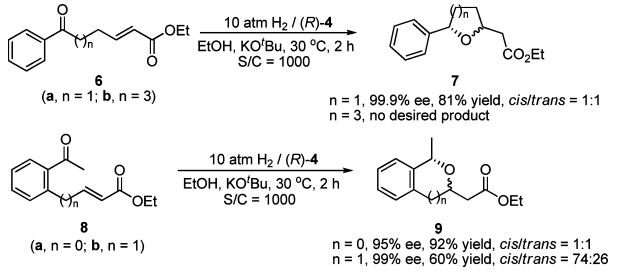
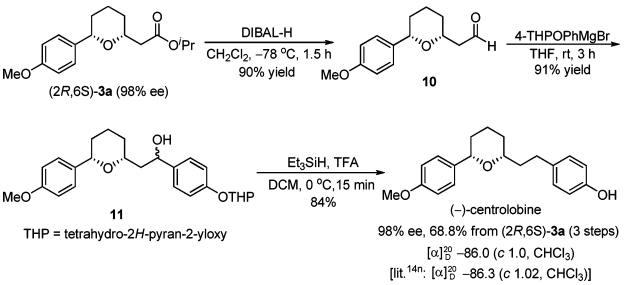
ketoester **6b** afforded the corresponding alcohol in 81% yield with 98% ee, along with an intramolecular Michael addition byproduct (see Supporting Information).

Scheme 2. Enantioselective Construction of Chiral Disubstituted Oxa-cyclic Ether Structures



We next studied the enantioselective synthesis of (−)-centrolobine starting from (2*R*,6*S*)-**3a**, the product of asymmetric hydrogenation/oxa-Michael cyclization of ketoester **1a** (Scheme 3). Although many protocols have been developed for the synthesis of (−)-centrolobine in recent years, highly efficient methods, especially asymmetric catalytic methods, from achiral starting materials are highly desirable.[14] Ester (2*R*,6*S*)-**3a** was reduced with diisobutylaluminum hydride (DIBAL-H) to aldehyde **10** in 90% yield. Aldehyde **10** was allowed to react with (4-(tetrahydro-2*H*-pyran-2-yloxy)phenyl)magnesium bromide (4-THPOC$_6$H$_4$MgBr) to produce alcohol **11**, which was then treated with Et$_3$SiH in the presence of trifluoroacetic acid (TFA) to afford the desired product in 76% yield (two steps). Thus, (−)-centrolobine was obtained in 68.8% yield in three steps from the catalytic asymmetric hydrogenation/oxa-Michael cyclization product (2*R*,6*S*)-**3a**.

Scheme 3. Enantioselective Synthesis of (−)-Centrolobine



In conclusion, we developed a method for efficient asymmetric hydrogenation of acrylate-containing arylketones catalyzed by chiral spiro ruthenium or iridium catalysts; this method permitted the enantioselective synthesis of chiral 2,6-*cis*-disubstituted tetrahydropyrans and related chiral oxa-cyclic ethers via a one-pot tandem asymmetric hydrogenation/oxa-Michael cyclization. The method was used for the highly efficient enantioselective synthesis of (−)-centrolobine.

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Supporting Information Available. Experimental procedures, spectral data for all new compounds, and the HPLC charts for the determination of the ee values. This material is available free of charge via the Internet at http://pubs.acs.org.

The authors declare no competing financial interest.