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Stereoselective Construction of *cis*-2,6-Disubstituted Tetrahydropyrans *via* the Reductive Etherification of δ-Trialkylsilyloxy Substituted Ketones: Total Synthesis of (—)-Centrolobine

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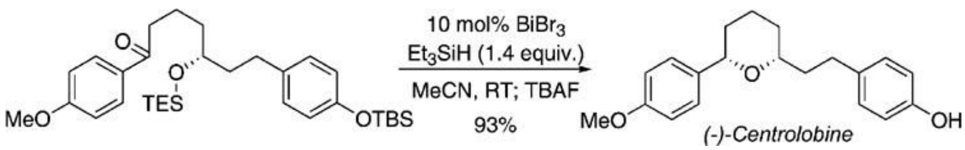
Abstract



The stereoselective *intra*molecular reductive etherification of δ-trialkylsilyloxy substituted ketones with catalytic bismuth tribromide and triethylsilane provides a convenient method for the construction of *cis*-2,6-disubstituted tetrahydropyrans. This method was highlighted in the key step of an expeditious total synthesis of the antibiotic, (—)-centrolobine.

The stereoselective construction of cyclic ethers remains a topical area of synthetic interest, particularly with respect to *C*-glycosides that are ubiquitous in biologically important natural products.[1] This may be attributed to their diverse and significant biological activity and the challenges associated with the design of stereochemically flexible approaches that provide access to either diastereoisomer. We have recently developed a two-component etherification reaction for the diastereoselective construction of *cis*- and *trans*-2,6-di- and trisubstituted tetrahydropyrans in excellent yield.[2,3] These studies provided compelling evidence for hydrogen bromide and bismuth oxybromide, derived from the *in situ* hydrolysis of bismuth tribromide, to be responsible for the catalysis.[4,5]

Herein, we now describe the extension of the *intra*molecular reductive etherification process using a series of *tert*-butylsilyloxy ketones **1** to highlight this strategy for the stereoselective construction of *cis*-2,6-disubstituted tetrahydropyrans **2** (Scheme 1). This work also provides additional support for Brønsted acid rather than Lewis acid catalysis, and highlights this transformation in an expeditious total synthesis of the antibiotic (—)-centrolobine (**4**).[6]

Recent studies by Bajwa and co-workers implicated triethylsilyl bromide as the Lewis acid catalyst in a series of *inter*molecular reductive etherification reactions with catalytic bismuth tribromide and triethylsilane.[7,8] We have demonstrated that the two-component etherification is catalyzed by hydrogen bromide and bismuth oxybromide, derived from the hydrolysis of bismuth tribromide.[2] This subtle difference in catalyst and similarity in the reagents prompted

Supporting Information Available: Experimental procedures and spectroscopic data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

the reinvestigation of the reductive etherification to determine which of these species was responsible for the catalysis.

The combination of bismuth tribromide and triethylsilane is known to generate elemental bismuth, hydrogen bromide, and triethylsilyl bromide.[8] Preliminary studies focused on the hypothesis that bismuth tribromide and triethylsilyl bromide provide an *in situ* source of hydrogen bromide, which then functions as the active Brønsted acid catalyst (Table 1, entries 1, 4, and 7). The addition of activated molecular sieves to each of these reagents, which should sequester only the HBr and water, completely suppresses the reaction (entries 2, 5, and 8).[10] Moreover, the addition of 2,6-di-*tert*-butyl-4-methylpyridine (DTBMP), which should neutralize any hydrogen bromide, leads to analogous results (entries 3, 6, and 9).[2] Hence, the reductive etherification reactions are consistent with Brønsted acid rather than Lewis acid catalysis.[11,12]

These experimental findings prompted the mechanistic revision of the original catalytic cycle proposed by Bajwa and co-workers, as outlined in Figure 1. The Brønsted acid formed through the reduction of bismuth trihalide is clearly not effectively buffered by the acetonitrile.[8] Protodesilylation of the δ-trialkylsilyloxy substituted ketone **i** catalyzed by the Brønsted acid should afford the hemiketal **iii**. Acid-catalyzed dehydration of **iii** should afford the intermediary oxocarbenium ion **iv**, which will be reduced to afford the *cis*-2,6-disubstituted tetrahydropyran **v**. The Brønsted acid can then be recycled through the hydrolysis of the trialkylsilyl halide, with the water derived from the dehydration of the hemiketal completing the catalytic cycle.

Table 2 summarizes the scope of the *intra*molecular reductive etherification. The δ-*tert*-butyldimethylsilyloxy ketones **1a—i** furnished the *cis*-2,6-disubstituted tetrahydropyrans **2a—i** in 82-97% yield with excellent diastereoselectivity (Scheme 1).[13] Interestingly, the reaction is remarkably tolerant to a wide array of substituents. For example aryl-, α-branched alkyl-, alkyl halide-, and alkene-containing substituents (entries 1-5), β-keto esters (entry 6), and hydroxymethyl derivatives (entries 7-9) are suitable substrates.

(—)-Centrolobine A (**4**) is an antibiotic that was isolated from the heartwood of *Centrolobium robustum* and from the stem of *Brosimum potabile* in the amazon rain forest.[6] Solladie and Rychnovsky have recently completed independent enantioselective total syntheses of this agent, and thereby determined its absolute configuration.[14] We envisioned that the reductive etherification using bismuth tribromide and triethylsilane would provide an expeditious route to this agent, as outlined in Scheme 2.

The initial approach to (—)-centrolobine (**4**) involved the examination of the reductive etherification of an aryl ketone **i** (Scheme 2; Route A). Enantioselective allylation of aldehyde **5**,[15] and protection of the resulting secondary alcohol (95% ee), furnished the triethysilyl ether **6** in 77% overall yield, as detailed in Scheme 3.[16] The alkene **6** was then subjected to cross-metathesis by using the *second-generation* Grubbs' catalyst, to afford the corresponding α,β-unsaturated ketone.[17] Selective hydrogenation of the alkene with Wilkinson's catalyst furnished the aryl ketone **7** in 74% yield from **6**. Treatment of the δ-triethylsilyloxy aryl ketone **7** with bismuth tribromide and triethylsilane at room temperature, followed by *in situ* removal of the *tert*-butyldimethylsilyl group afforded (—)-centrolobine (**4**) in 93% yield, with excellent diastereoselectivity. Synthetic (—)-centrolobine (**4**) was identical in all respects with the reported spectral data for the natural substance (^{1}H/^{13}C NMR and IR), including optical rotation $[\alpha]^{22}_{D}$ −90.3 (c = 0.88, $CHCl_3$) {lit.[6b] $[\alpha]_D$ −92.2 (c = 1, $CHCl_3$)}. Overall, this total synthesis was accomplished in 5 steps from aldehyde **5**, in 53% overall yield, making it the most efficient route developed to date.

The alternative approach to (—)-centrolobine (**4**) involved the reductive coupling of a benzylic triethylsilyl ether **ii** (Scheme 2; Route B). Treatment of the ketone **8**, which was prepared in 4 steps by using an analogous reaction sequence, with bismuth tribromide and triethylsilane furnished none of the desired product. This observation is presumably the result of the solvolysis of the activated benzylic triethylsilyl ether and/or alcohol formed through protodesilylation.

In conclusion, we have demonstrated that the *intra*molecular reductive etherification using bismuth tribromide and triethylsilane provides a versatile route for 2,6-disubstituted tetrahydropyrans. These studies also provide additional support for the notion that the hydrolysis of bismuth tribromide leads to the generation of hydrogen bromide, which functions as a Brønsted acid catalyst. Finally, this methodology was highlighted in an expeditious total synthesis of the antibiotic, (—)-centrolobine.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgment

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(9). The addition of water (100 mol %) afforded the cyclic ether **2** in quantitative yield and with excellent selectivity (entry 4). This further supports the notion that triethylsilyl bromide is not the active catalyst

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(11). Interestingly, the nature of the triorganosilyloxy protecting group is inconsequential in terms of the overall reaction efficiency and selectivity (TES ~ TBS ~ TIPS)

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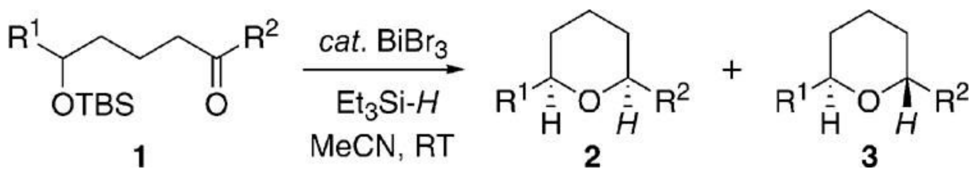

Scheme 1.

General Strategy for the Stereoselective Construction of *cis*-2,6-Disubstituted Tetrahydropyrans with an *Intra*molecular Reductive Etherification

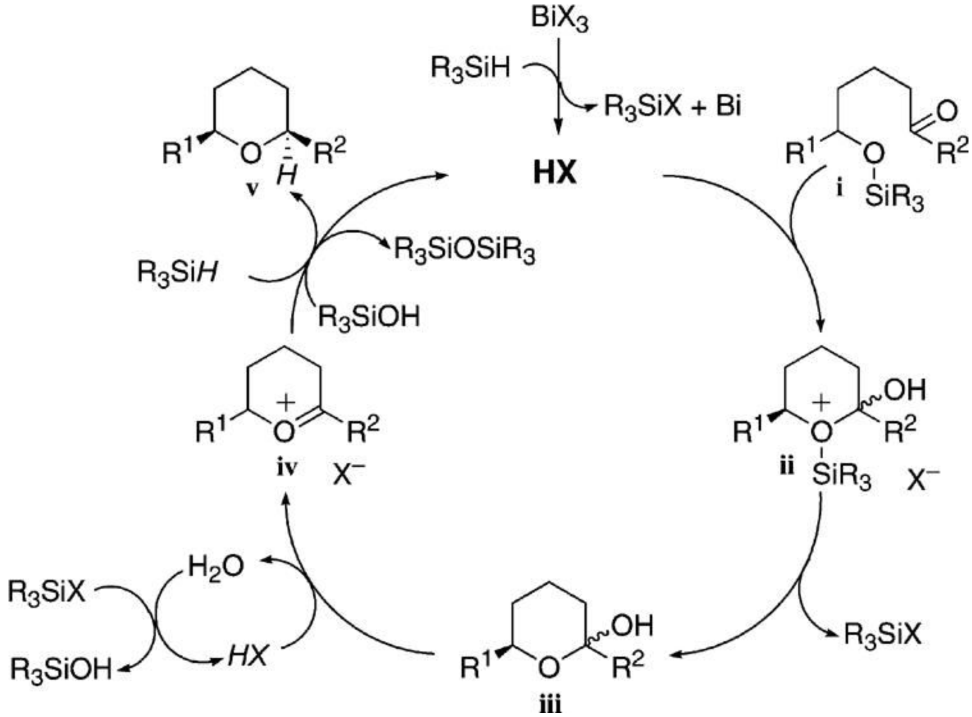

Figure 1.
Proposed catalytic cycle for the reductive etherification with bismuth trihalides and trialkylsilanes.

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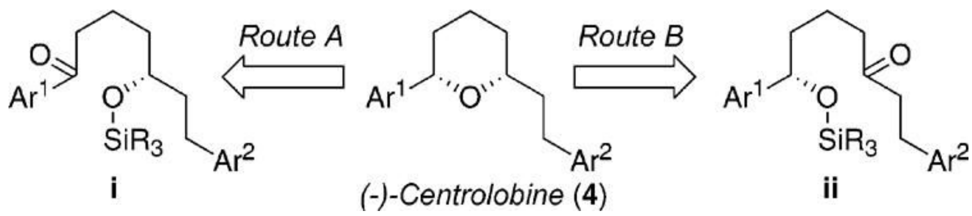
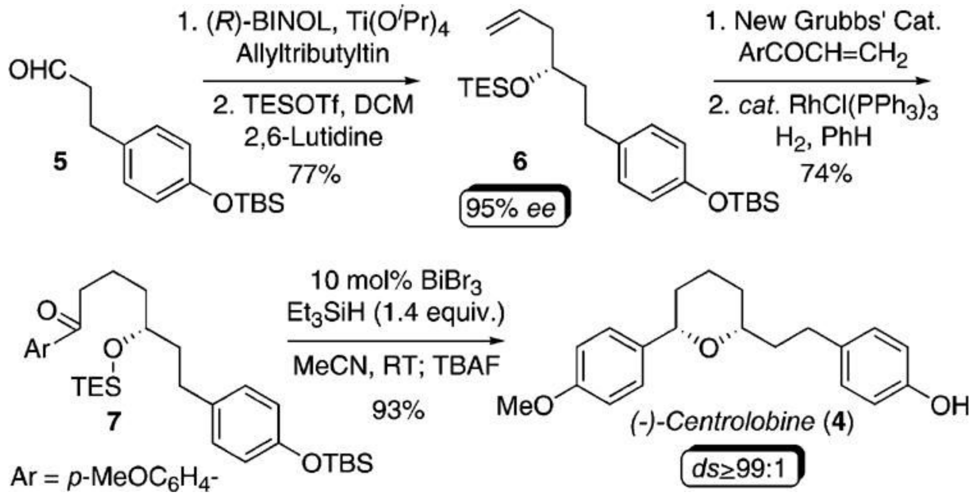


Scheme 2.
Retrosynthetic Analysis for (—)-Centrolobine; Potential Reductive Etherification Reactions



Scheme 3.
Stereoselective Synthesis of (—)-Centrolobine with an *Intra*molecular Reductive Etherification

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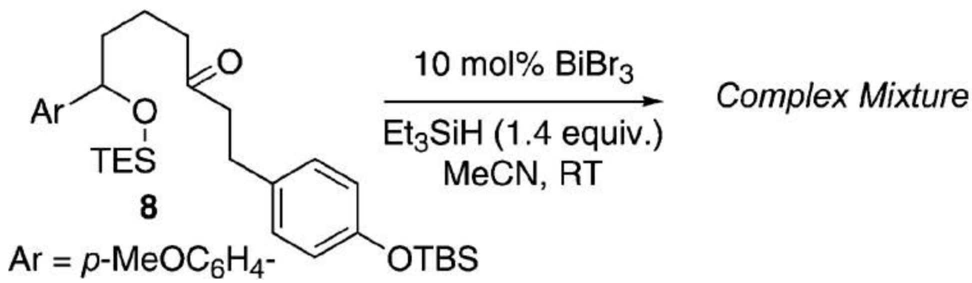

Scheme 4.
Attempted Reductive Etherification with the Benzylic Triethylsilyl Ether **8**

Table 1

Elucidation of the Role of Bismuth Tribromide in the *Intra*molecular Reductive Etherification Reaction (Scheme 1; **1a**, $R^1 = PhCH_2$, R^2) Ph)[a]

entry	catalyst	additive	mol %	ratio of 2a:3a[e]	yield (%)[f]
1	$BiBr_3$	—	5	≥99:1	97
2	"	4Å Sieves[b]	"	NA	0
3	"	DTBMP[c]	"	NA	0
4	TESBr[9]	—	15[d]	≥99:1	99
5	"	4Å Sieves[b]	"	NA	0
6	"	DTBMP[c]	"	NA	0
7	HBr	—	15[d]	≥99:1	99
8	"	4Å Sieves[b]	"	NA	0
9	"	DTBMP[c]	"	NA	0

[a]All the reductive etherification reactions were carried on a 0.1 mmol reaction scale in acetonitrile at room temperature with 1.2 equiv of triethylsilane.

[b]Molecular sieves were activated at 150 °C under high vacuum.

[c]20 mol % based on **1a**.

[d]Assuming bismuth tribromide can yield up to 3 equiv of hydrogen bromide and/or triethylsilyl bromide.

[e]Ratios of diastereoisomers were determined by GLC on the crude reaction mixtures.

[f]GLC yields.

Table 2

Scope of the Diastereoselective *Intra*molecular Reductive Etherification Reactions (Scheme 1; $R^1 = PhCH_2$)[a]

entry	*tert*-butylsilyloxy ketone, R^2 =	1	ratio of 2:3[b,c]	yield (%)[d]
1	Ph	**a**	≥99:1	97
2	Me	**b**	≥99:1	90
3	*i*Pr	**c**	≥99:1	95
4	$(CH_2)_6Br$	**d**	≥99:1	96
5	$CH_2CH{=}CH_2$	**e**	≥99:1	95
6	CH_2CO_2Et	**f**	≥99:1	97[e]
7	CH_2OH	**g**	≥99:1	82[f]
8	CH_2OBz	**h**	≥99:1	93
9	CH_2OBn	**i**	≥99:1	91

[a] All the reductive etherification reactions were carried on a 0.2 mmol reaction scale in acetonitrile at room temperature with 5 mol % of $BiBr_3$ and 1.2 equiv of triethylsilane.

[b] Ratios of regioisomers were determined by GLC.

[c] The stereochemical assignment was made with use of an NOE in each case.

[d] Isolated yields.

[e] 10 mol % of $BiBr_3$ and 2.0 equiv of triethylsilane.

[f] 20 mol % of $BiBr_3$ and 2.0 equiv of triethylsilane.