# Formation of Tetrahydrofuran from Homoallylic Alcohol via a Tandem Sequence: 2-Oxonia [3,3]-Sigmatropic Rearrangement/Cyclization Catalyzed by $In(OTf)_3$

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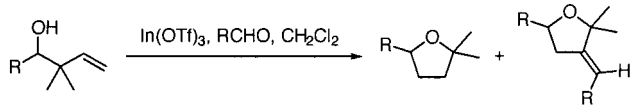
In the past decade, indium(III) complexes have enjoyed remarkably widespread use as efficient Lewis acid catalysts for various carbon−carbon bond formation reactions and important synthetic transformations.[1] In accordance with the recent surge of interest in metal triflates,[2] $In(OTf)_3$ has emerged as a promising catalyst in the past few years. The $Sn(OTf)_2$-catalyzed conversion of $\gamma$-adduct homoallylic alcohol to the corresponding $\alpha$-adduct was reported by Nokami's group recently.[3] Nevertheless, unsatisfactory results in the case of prenyl adducts limited its applicability in view that the prenyl moiety is featured as a key structural fragment in terpenoids, as well as their synthetic precursors.[4] This encouraged us to explore modifications by employing $In(OTf)_3$, a stronger Lewis acid, instead. Herein we describe an unexpected formation of tetrahydrofuran during the course of exploration.

In our initial study, a solution of homoallylic alcohol **1a**[5] and the corresponding aldehyde (0.1 equiv) in dichloromethane was stirred with a catalytic amount of $In(OTf)_3$ (0.1 equiv) at room temperature for 10 days (Table 1, entry 1). The crude NMR indicated that 70% of the starting material was consumed, with the appearance of two new sets of *gem*-dimethyl signals ($\delta$ 1.32, 1.23 and 1.27, 1.24), neither of which corresponds to those expected for the desired $\alpha$-adduct.[3b] Chromatographic separation gave two products **2a** and **3a**, which were subjected to extensive spectroscopic studies. To our surprise, both compounds were found to possess an unexpected 2-substituted 5,5-dimethyltetrahydrofuran skeleton. Since this moiety is featured in a large number of biologically important natural products,[6] and the development of synthetic methods is needed,[7] the reaction was studied in detail (Table 1).

**Table 1.** Formation of Tetrahydrofuran from Homoallylic Alcohol Catalyzed by $In(OTf)_3$[a]




**1** **2** **3**

| entry | | R | $In(OTf)_3$/ equiv | RCHO/ equiv | *T*/ °C | time/ h | yield[b]/ % (**2**:**3**)[c] |
|---|---|---|---|---|---|---|---|
| 1 | **a** | $PhCH_2CH_2$ | 0.1 | 0.1 | 25 | 240 | 54 (81:19) |
| 2 | **a** | $PhCH_2CH_2$ | 0.2 | 0.1 | 25 | 192 | 70 (59:41) |
| 3 | **a** | $PhCH_2CH_2$ | 0.1 | 0.1 | 40 | 14 | 56 (70:30) |
| 4 | **a** | $PhCH_2CH_2$ | 0.1 | 1.0 | 40 | 14 | 60 (3:97) |
| 5 | **b** | Ph | 0.1 | 0.1 | 40 | 14 | 28[e] (72:28) |
| 6 | **b** | Ph | 0.1 | 1.0 | 40 | 14 | 66 (3:97) |
| 7 | **c** | $CH_3(CH_2)_7$ | 0.1 | 0.1 | 40 | 14 | 59 (75:25) |
| 8 | **c** | $CH_3(CH_2)_7$ | 0.1 | 1.0 | 40 | 14 | 58 (7:93) |
| 9 | **d** | *p*-$ClC_6H_4$ | 0.1 | 0.1 | 40 | 14 | 61 (81:19) |
| 10 | **d** | *p*-$ClC_6H_4$ | 0.2 | 0.5 | 40 | 14 | 57 (38:62) |
| 11 | **d** | *p*-$ClC_6H_4$ | 0.1 | 1.0 | 40 | 14 | 82 (27:73)[d] |

[a] Strem Chemicals, Inc. [b] Combined yield based on **1**. [c] Determined by $^1H$ NMR. [d] In addition, eliminated rearrangement product **5d′** (8%) was isolated. [e] Low isolated yield due to volatile nature of **2b**.

It was found that by increasing the amount of $In(OTf)_3$ to 0.2 equiv, the conversion of **1a** to **2a** and **3a** can be driven to completion, albeit with a compromise in the selectivity (entry 2). As a result, efforts were directed toward improving the selectivity of this method. It is noteworthy that either **2** or **3** can be made the major product by simply altering the reaction condition. When the reaction was conducted in the presence of a catalytic amount of $In(OTf)_3$ (0.1 equiv) and aldehyde (0.1 equiv) at 40 °C for 14 h, **2** was formed preferentially (ratio up to 81:19, entry 9). On the other hand, upon increasing the amount of aldehyde to 1 equiv, **3** became the major product, with selectivity up to 97% (entry 4). In addition, the double bond in **3** was determined by NOESY to have an (*E*) geometry in all cases. Nevertheless, no cyclization was observed with 1-alkyl-2-methyl-3-butenols and 1-alkyl-3- butenols, wherein only the corresponding $\alpha$-adduct homoallylic alcohols were obtained.[8]

On the basis of the above observations, we postulate that the reaction sequence involves first an $In(OTf)_3$-promoted conversion of the homoallylic alcohol ($\gamma$-adducts) **1** to the corresponding $\alpha$-adduct **5** via a 2-oxonia [3,3]-sigmatropic rearrangement[3,7c,7d] of oxocarbenium **4A**. This is followed by a rapid intramolecular *oxyindiation*[9] with $In(OTf)_3$ to give the tetrahydrofuranyl-indium species **6** (Scheme 1). Trapping **6** with a proton source would furnish **2**, while alternative nucleophilic attack at the parent aldehyde would provide **3** through elimination. The involvement of $\alpha$-adduct **5** as an intermediate was supported by the fact that

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(8) These results will be published elsewhere in due time.

(9) The term "oxyindiation" refers to the additive incorporation of an oxygen and indium across a double bond. Further mechanistic studies are required to verify this tentatively presumed pathway.

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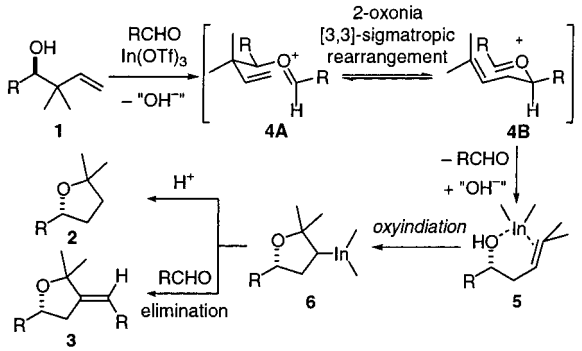
**Scheme 1.** Postulated Reaction Pathway



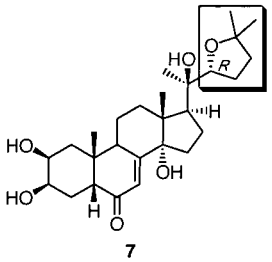
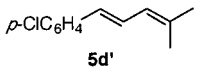




**Figure 1.** Structure of shidasterone.

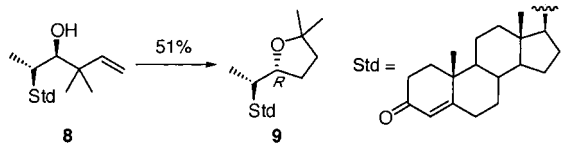
4-methyl-1-phenylpent-3-en-1-ol[3b] (**5b**) gave the same product **3b** when subjected to the conditions of entry 6. In addition, the isolation of byproduct **5d′** in entry 11 provided further evidence for this.




Shidasterone (**7**), an ecdysteroid first isolated in 1969,[6b] has attracted renewed synthetic interest due to recent reports of its antitumor activity,[10] in addition to its role as an insect molting hormone. The structure of shidasterone features a 5,5-dimethyltetrahydrofuran-2-yl fragment attached at C-22 in an anti-Cram[11] manner (Figure 1).

According to our postulated reaction pathway, its side chain can be derived stereospecifically from the corresponding Cram $\gamma$-adduct homoallylic sterol, thus furnishing an efficient synthetic route. Explorations were conducted on homoallylic sterol **8**,[12] and an optimized procedure (**8** 1.0 equiv, parent aldehyde[13] 0.1 equiv, $In(OTf)_3$ 0.15 equiv, 40 °C, 48 h) was adopted to give **9** in 51% yield (Scheme 2), together with 21% of undesired **3** (R = Std). The stereochemistry of C-22 was determined to be the desired (*R*)-configuration by single-crystal X-ray diffraction analysis.[14] This provided strong support for the involvement of a 2-oxonia [3,3]-sigmatropic rearrangement as proposed in Scheme 1. In addition, the reaction displays excellent functionality tolerance toward the A ring enone. With this, we established the potential applicability of the method to natural product synthesis.

**Scheme 2.** Application to Synthesis of the Steroid Side Chain




In summary, a tandem 2-oxonia [3,3]-sigmatropic rearrangement/cyclization sequence catalyzed by $In(OTf)_3$ was discovered in our laboratory, and subsequently developed as an efficient method for the selective formation of tetrahydrofuran **2** or **3** in a stereospecific fashion, from the corresponding $\gamma$-adduct homoallylic alcohol. The formation of **3** suggested the involvement of a tetrahydrofuranyl-indium species, plausibly formed via an intramolecular oxyindiation of the intermediate α-adduct **5** generated in situ. This method opens up a new avenue for the stereospecific synthesis of cyclic ethers, and has been demonstrated in the construction of the tetrahydrofuran moiety present in the shidasterone side chain.

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**Supporting Information Available:** Complete experimental details, including characterization data for all new compounds, and copies of COSY, NOESY, HMQC, and HMBC NMR spectra of compound **3a** (PDF); X-ray crystal data for **9** (CIF). This material is available free of charge via the Internet at http://pubs.acs.org.

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(13) 4-Pregnene-20$\beta$-carboxaldehyde-3-one was purchased from Sigma Chemical Co.

(14) X-ray data for **9**: $C_{27}H_{42}O_2$; fw = 398.61; orthorhombic; space group $P2_12_12_1$; $a$ = 6.0506(6) Å, $b$ = 17.507(2) Å, $c$ = 22.199(2) Å; $V$ = 2351.4(4) Å 3; $Z$ = 4; $R1$ = 0.0721, $wR2$ = 0.1474, GOF = 0.981 for 6804 observations with $I > 2(I)$.