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Selective Lewis Acid Catalyzed Transformation (γ-Butyrolactone versus Cyclopropane) of 2-Methoxy-4-benzyltetrahydrofuran Derivatives. Efficient Synthesis of Lignan Lactones

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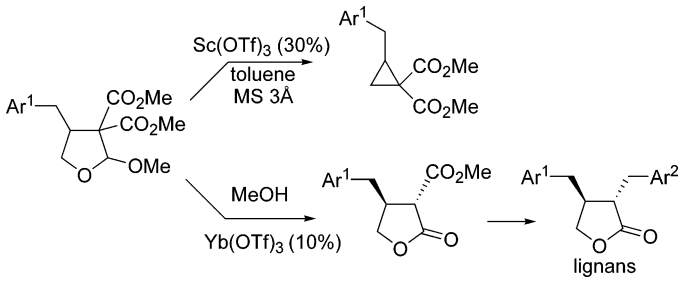
ABSTRACT



A short synthesis of lactone lignans exploiting a three-component coupling strategy is presented using a new Lewis acid catalyzed ring-opening/cyclization reaction of 2-methoxytetrahydrofuran derivatives 4 leading to γ-butyrolactones as a key step. By simply changing the reaction conditions, it was possible, from the same substrates 4, to obtain selectively cyclopropane derivatives.

Lactone lignans are a class of natural products that have received considerable interest because of their biological and medicinal properties.[1] Several strategies for the synthesis of dibenzyl butyrolactone lignans **1** have been reported (Figure 1).[2] Among them, the alkylation of β-substituted γ-butyrolactones **2** with an appropriate benzylic halide is the most widely used.[3] The major drawbacks of this synthetic route are the necessity to add an undesirable complexing agent such as the carcinogenic hexamethylphosphoric triamide (HMPA) to assist the alkylation step and to carry out this reaction under low-temperature conditions.[3d,4]

For some time now, we have been interested in developing new processes to form several carbon−carbon and carbon−

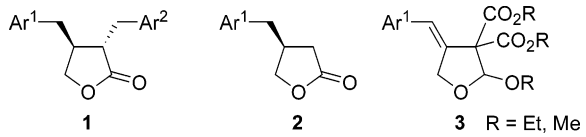


Figure 1. Natural lignans and strategic synthons.

(1) (a) Cho, M. K.; Jang, Y. P.; Kim, Y. C., Kim, S. G. *Int. Immunopharm.* **2004**, *4*, 1419−1429. (b) Midori, T.; Takao, K.; Katsuko, K.; Harukuni, T.; Hoyoru, N. *Cancer Lett.* **2000**, *158*, 53−59. (c) Sibi, M. P.; Liu, P.; Johnson, M. D. *Can. J. Chem.* **2000**, *78*, 133−138. (d) Li, N.; Wu, J. L.; Sakai, J. I.; Ando, M. *J. Nat. Prod.* **2003**, *66*, 1421−1426. (e) Ayreas, D. C.; Loike, J. D. *Chemistry & Pharmacology of Natural Products. Lignans, Chemical, Biological and Clinical Properties*; Cambridge University Press: New York, 1990. (f) Usia, T.; Watabe, T.; Kadota, S.; Tesuka, Y. *J. Nat. Prod.* **2005**, *68*, 64−68.

(2) For review, see: Raffaelli, B.; Hoikkala, A.; Leppälä, E.; Wähälä, K. *J. Chromatogr. B* **2002**, *777*, 29−43.

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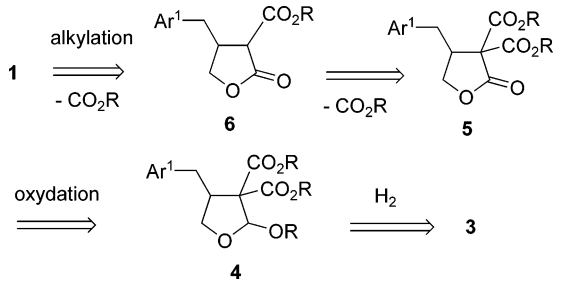
heteroatom bonds in one reaction.[5] In line with this, we recently reported an efficient palladium-catalyzed three-component synthesis of 2-methoxy-4-arylidenetetrahydrofuran derivatives **3** by a one-pot coupling reaction of commercially available or easily accessible propargyl alcohols, diethyl methoxymethylenemalonate, and aryl halides. This strategy was successfully applied to the synthesis of the lignan antibiotic burseran.[6]

It was then envisaged to extend this methodology to the synthesis of dibenzyl butyrolactone lignans **1**. Our approach to this class of compounds synthesis is outlined in Scheme 1. It was anticipated that hydrogenation of **3** would furnish

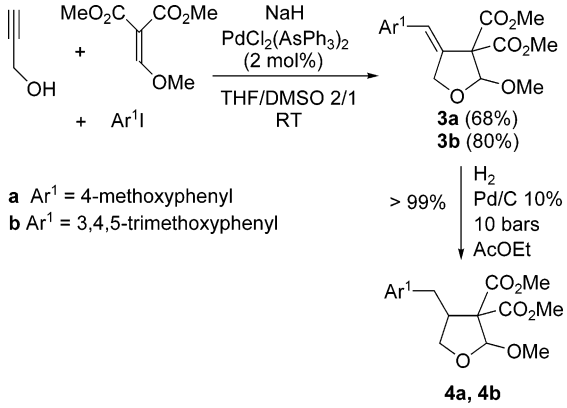
Scheme 1. Retrosynthetic Analysis



4, which after conversion of the protected lactol into lactone **5** and subsequent decarbalkoxylation would provide the desired key intermediate **6**. A significant advantage to this methodology is that alkylation of **6** would be highly facilitated by the presence of the ester group which could be removed in a subsequent step.

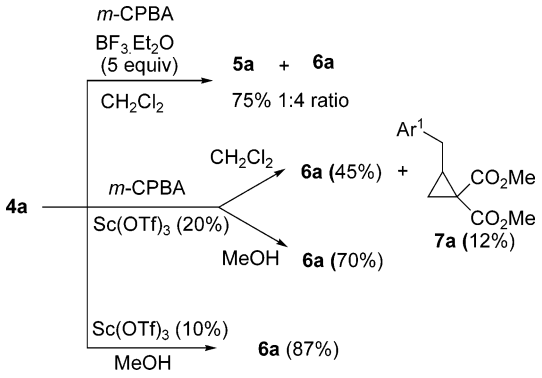
Our investigations began with the preparation of acetals **3a** and **3b** which were readily available on a multigram scale using a slight modification of our previously reported procedure.[6,7] Hydrogenation of **3a** and **3b** by using palladium on carbon (Pd/C) provided the corresponding reduced products **4a** and **4b** isolated in the form of a single isomer in nearly quantitative yield (Scheme 2). Subsequent transformation of the lactol ether in **4a** into the corresponding lactone was envisaged through the oxidative Grieco method.[8]

Scheme 2. Synthesis of Furans **4**



However, upon treatment of compound **4a** in CH_2Cl_2, with *m*-CPBA in the presence of catalytic amounts of boron trifluoride (10 mol %) only unreactive starting material was recovered. Surprisingly, when the reaction was performed in the presence of a large excess of $BF_3{\cdot}Et_2O$ (5 equiv), an inseparable mixture of the expected lactone **5a** and of the targeted lactone **6a** (75%) was obtained in a 1:4 ratio (Scheme 3).

Scheme 3. Obtention of Lactone **6a** from Furan **4a**



Modifications of the experimental conditions by introducing a catalytic amount (20 mol %) of $Sc(OTf)_3$ in place of the conventional Lewis acid $BF_3{\cdot}Et_2O$ did not afford the expected product **5a**.[9] Under these conditions, the lactone **6a** was isolated in 45% yield along with the cyclopropanic compound **7a** (12% yield). When the same reaction was carried out in methanol, under reflux for 4 days, lactol ether **4a** was directly converted to lactone **6a** in a single step and in 70% yield. We further found that a simple treatment of **4a** with 10 mol % of $Sc(OTf)_3$ in methanol at reflux for 10 h provided the lactone **6a** in 87% yield.

(3) (a) Itoh, T.; Chika, J.; Takagi, Y.; Nishiyama, S. *J. Org. Chem.* **1993**, *58*, 5717−5723. (b) Yang, L.-M.; Lin, S.-J.; Yang, T.-H.; Lee, K.-H. *Bioorg. Med. Chem. Lett.* **1996**, *6*, 941−944. (c) Bode, J. W.; Doyle, M. P.; Protopopova, M. N.; Zhou, Q.-L. *J. Org. Chem.* **1996**, *61*, 9146−9155. (d) Kamlage, S.; Sefkow, M.; Pool-Zobel, B. L.; Peter, M. G. *Chem. Commun.* **2001**, 331−332. (e) Koul, S.; Singh, B.; Taneja, S. C.; Qazi, G. N. *Tetrahedron* **2003**, *59*, 3487−3491. (f) Isemori, Y.; Kobayashi, Y. *Synlett* **2004**, 1941−1944.

(4) Mäkelä, T. H.; Wähälä, K. T.; Hase, T. A. *Steroids* **2000**, *65*, 437−441.

(5) (a) Balme, G.; Bouyssi, D.; Monteiro, N. Metal-Catalyzed Multicomponent Reactions. In *Multicomponent Reactions*; Zhu, J., Bienaymé, H., Eds.; Wiley VCH: Weinheim, 2005; pp 224−276. (b) Balme, G.; Bossharth, E.; Monteiro, N. *Eur. J. Org. Chem.* **2003,** 4101−4111. (c) Balme, G.; Bouyssi, D.; Lomberget, T.; Monteiro, N. *Synthesis* **2003**, 2115−2134.

(6) Garçon, S.; Vassiliou, S.; Cavicchioli, M.; Hartmann, B.; Monteiro, N.; Balme, G. *J. Org. Chem.* **2001**, 66, 4069−4073. See also: Doe, M.; Shibue, T.; Haraguchi, H.; Morimoto, Y. *Org. Lett.* **2005**, *7*, 1765−1768.

(7) More practically, $PdCl_2(AsPPh_3)_2$ was used for this large-scale synthesis instead of in situ *n*-BuLi reduction of $PdCl_2(PPh_3)_2$ which was employed in the initial paper.

(8) Grieco, P.; Oguri, T.; Yokoyama, Y. *Tetrahedron Lett.* **1978**, *19*, 419−420.

(9) $Sc(OTf)_3$ is known to be an effective catalyst to generate a reactive oxocarbenium ion from an acetal; see: Heaney, H.; Simcox, M. T.; Slawin, A. M. Z.; Giles, R. G. *Synlett*, **1998**, 640−642. Kobayashi, S.; Sugiura, M.; Kitagawa, H.; Lam, W. W.-L. *Chem. Rev.* **2002**, *102*, 2227−2302.

A series of Lewis acids was then surveyed to determine which were the most effective for this reaction, and the results are summarized in Table 1.

Table 1. Screening of Lewis Acids

entry	Lewis acid	equiv	time (h)	yield (%)
1	$BF_3{\cdot}Et_2O$	2.0	10	*a*
2	CF_3CO_2H	2.0	24	*a*
3	$Zn(OTf)_2$	0.1	24	9[b]
4	$Cu(OTf)_2$	0.2	12	70[b]
5	$Sc(OTf)_3$	0.1	10	87
6	$Yb(OTf)_3$	0.1	4	94
7	$Yb(OTf)_3$	0.02	40	92
8	$Yb(OTf)_3$ MS 3 Å	0.1	48	*a*

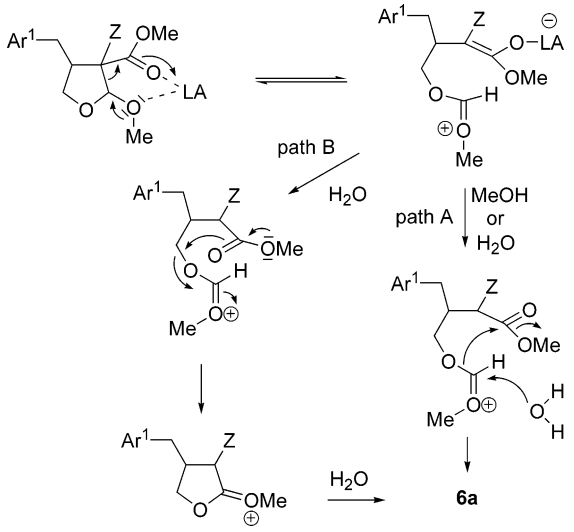
[a] No reaction. [b] Starting material was partially recovered.

Conventional Lewis acid ($BF_3{\cdot}Et_2O$) as well as strong protic acids (CF_3CO_3H) were not effective for this reaction (Table 1, entries 1 and 2). Addition of metal triflate salts such as $Zn(OTf)_2$ provided a small amount of the lactone with most of the starting material recovered (Table 1, entry 3). An improvement in the yield was observed with $Cu(OTf)_2$ (Table 1, entry 4). Of these metals, Yb(III) complexes gave the best results in this reaction. Indeed, **6a** was isolated in 94% yield when using 10 mol % of $Yb(OTf)_3$ in methanol at reflux for 4 h (Table 1, entry 6). Decreasing the amount of catalyst to 2 mol % allowed us to obtain lactone **6a** in 92% yield but required a prolonged reaction time to complete the reaction (Table 1, entry 7). It should be emphasized that the starting material **4a** was entirely recovered when the reaction was performed in the presence of 10 mol % of $Yb(OTf)_3$ and of molecular sieves as drying agent (Table 1, entry 8). Using the optimized conditions, **4b** was readily transformed in lactone **6b** in a very good yield (93%).

A plausible mechanism for this direct conversion of **4a** to **6a** is proposed in Scheme 4. Lewis activation of the acetal presumably promotes ring cleavage of the 2-methoxytetrahydrofuran and generates a stabilized malonic enolate and an oxonium species. Two routes (path A and path B) could be then proposed for the lactone ring formation. In path A, the oxonium species could be captured by methanol or by water, present as contaminant in the reaction mixture. The resulting alcohol could then attack one of the ester groups to give **6a**. Lactone **6a** could also arise from the intramolecular cyclization of one of the esters onto the reactive carbon bearing the leaving group as depicted in path B.[10]

Next, we examined the alkylation of lactone **6a** with a benzyl halide such as 3,4-methylenedioxybenzyl bromide. This was accomplished in 90% yield when the reaction was performed in DMF at room temperature in the presence of K_2CO_3 as base.[11] Decarbalkoxylation of the resulting lactone

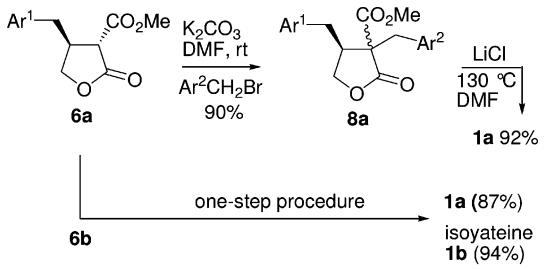
Scheme 4. Proposal for the Formation of Lactone **6a**



8a under Krapcho's condition[12] (NaCl, DMF, 130 °C) afforded methyl ether of chamalignolide **1a** which was obtained predominantly as the *trans* alkylated product (85:15) in 92% yield.[13] Equilibration with DBU (CH_2Cl_2, rt) afforded **1a** as a highly enriched isomer (19:1).

At this point, a more direct alkylation/decarbalkoxylation method was envisaged. The two steps were conducted sequentially in the same reaction vessel without isolation of the intermediate by adding LiCl (5 equiv) and water (2 equiv) to the resulting product of the alkylation reaction. Heating the mixture at 130 °C for 4 h resulted in the formation of dibenzyl butyrolactone **1a** as a 85:15 mixture of diastereoisomers in 87% yield (Scheme 5). Application of the same

Scheme 5. One-Step Alkylation−Decarboxylation Sequence



1a and **1b** were isolated as a trans/cis ratio : 85/15

one-pot procedure to lactone **6b** resulted in the formation of isoyateine **1b** in 94% yield. This natural lignan **1b** has been obtained in only four synthetic steps and in an excellent 69% overall yield. The spectra of **1b** (^1H NMR, ^{13}C NMR) were in accordance with those reported in the literature.[14]

(10) Christie, S. D. R.; Davoile, R. J.; Elsegood, M. R. J.; Fryatt, R.; Jones, R. C. F.; Pritchard, G. J. *Chem. Commun.* **2004**, 2474−2475.

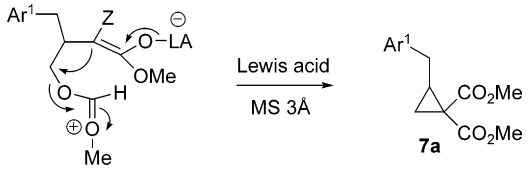
(11) **8a** was isolated as a single isomer, but the stereochemistry was not determined.

(12) Krapcho, A. P.; Lovey, A. J. *Tetrahedron Lett.* **1973**, *14*, 957−960.

(13) Chamalignolide is a new lignan recently isolated from the heartwood of *Chamaecyparis obtusa* var. *formosana*; see: Kuo, Y.-H.; Chen, C.-H., Lin, Y.-L. *Chem. Pharm. Bull.* **2002**, *50*, 978−980. Removal of the *O*-methyl group was recently carried out on related dibenzylbutyrolactone lignans; see ref 3f.

On the basis of the preceding results (Scheme 3), it was envisioned that this strategy could also be applied to the synthesis of cyclopropanic compounds **7**. These cyclized products would arise from an intramolecular enolate ester attack on the carbon bearing the leaving group. We suspected that water, present as a contaminant in the reaction mixture, may be an important factor that influences the outcome of the reaction (lactone formation versus cyclopropanation). Consequently, various reactions were performed under anhydrous conditions by adding molecular sieves 3 Å (MS 3 Å) as drying reagent. The conditions and results are shown in Table 2. Under the strictly dried conditions, mainly unreacted starting material was recovered when the reaction was performed in CH_2Cl_2 at reflux (Table 2, entries 1 and 2). In marked contrast, the reaction conducted in toluene at reflux in the presence of 30 mol % of $Yb(OTf)_3$ resulted in the exclusive formation of the expected cyclopropanic substrate **7a** in 65% yield (Table 2, entry 3). The yield was improved when $Sc(OTf)_3$ was used instead of $Yb(OTf)_3$ as a catalyst (Table 2, entry 4). Under these conditions, the starting material was completely consumed and the cyclopropanic substrate **7a** was formed in high yield (86%). With lactol ether **4b**, the corresponding cyclopropanic substrate **7b** was also formed and best results were obtained when the reaction was performed in toluene at 70 °C for 4 h (Table 2, entry 5).[15]

Table 2. Selective Formation of Cyclopropane **7a**



entry	furan	conditions[a]	time (h)	yield (%)
1	**4a**	$Sc(OTf)_3$ (20%), CH_2Cl_2, reflux	24	12[b]
2	**4a**	$Yb(OTf)_3$ (20%), CH_2Cl_2, reflux	24	0[b]
3	**4a**	$Yb(OTf)_3$ (30%), toluene, reflux	96	65
4	**4a**	$Sc(OTf)_3$ (30%), toluene, reflux	24	86
5	**4b**	$Sc(OTf)_3$ (30%), toluene, 70 °C	4	65

[a] All reactions were conducted in the presence of MS 3 Å. [b] Starting material was recovered.

In summary, we have developed a convergent, high yielding and practical synthesis of dibenzylbutyrolactone lignans based on the one-pot Lewis acid $Yb(OTf)_3$-catalyzed ring opening/cyclization reaction of the readily available functionalized 2-methoxy-4-benzyltetrahydrofuran derivatives **4**. Additionally, by simply changing the reaction conditions, we have demonstrated that it is possible from the same substrates **4** to obtain selectively functionalized cyclopropanic compounds.

Supporting Information Available: Detailed synthetic procedures and spectroscopic characterization of new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

OL050690H

(14) Badheka, L. P.; Prabhu, B. R.; Mulchandani, N. B. *Phytochemistry* **1986**, *25*, 487−489.

(15) When reaction was conducted at toluene reflux, degradation of the starting material was observed.