A short synthesis of biologically active lignan analogues

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β-Benzyl-γ-butyrolactones were synthesized in four transition metal catalysed reactions from butynediol, and alkylated to afford new, biologically active lignan analogues.

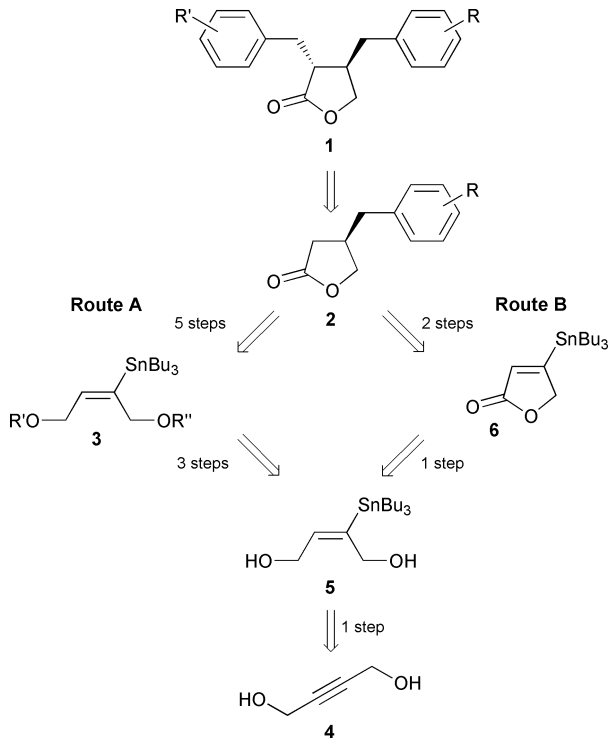
Lignans, dimers of phenylpropenes, are ubiquitous secondary plant metabolites.[1] They exhibit notable biological activities, in particular antiviral,[2] cytotoxic[3] and canceroprotective[4] properties. Many lignan syntheses have been reported in the past.[1,5] Two different strategies were most frequently followed for the synthesis of butyrolactone lignans **1**: 1. oxidative dimerization of *p*-hydroxycinnamic acids[6] and 2. alkylation of β-benzyl-γ-butyrolactones **2**.[7] Following these routes, between 6 and 13 steps were necessary to obtain this class of lignans. We reported recently the Stille coupling[8] of unsymmetrically protected 2-tributylstannylbuten-1,4-diols **3** with a variety of benzyl bromides.[9] This coupling reaction was the key step for the preparation of lactones **2** from butynediol **4** (Scheme 1, Route A) but several protecting group manipulations were necessary and the overall yields were low (6–15%). Thus, a regioselective oxidation of 2-tributylstannylbut-2-en-1,4-diol (**5**) to lactone **6** was desirable for a short synthesis of lactone **2** (Scheme 1, Route B). Herein we report the synthesis of lactone **2** using only four transition metal catalysed reactions. Key step was the hitherto unknown, regioselective oxidation of diol **5** to lactone **6**.[10]

The palladium catalysed *cis*-selective addition of tributylstannane to butynediol **4** is well documented.[11] The quality of diol **4** was crucial in this step. Purification of this compound prior to its use was necessary to obtain diol **5** in 92% yield (Scheme 2).

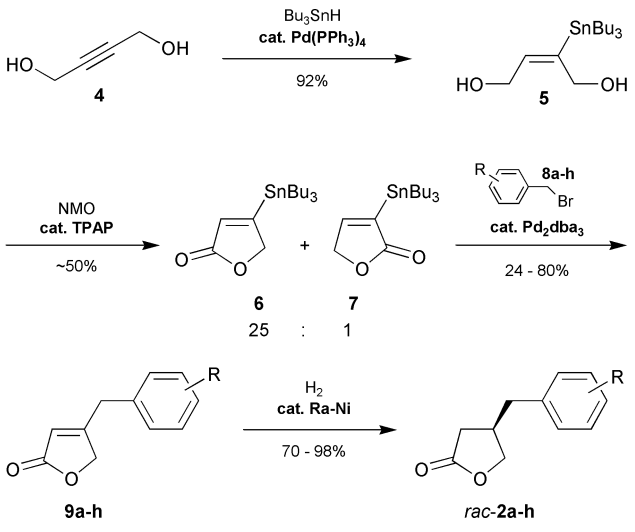
The hydroxy group at C(4) of diol **5** can be regioselectively protected using bulky silyl groups like the TBDMS group.[12] We assumed that selective oxidation of this hydroxy group may occur if a sterically demanding oxidation reagent like TPAP[13] in conjunction with NMO was employed. The selective oxidation of a primary hydroxy group in the presence of a secondary using this oxidation system was reported by Bloch and Brillet[14] but a regioselective oxidation of one of two primary hydroxy groups has not been published yet.

Treatment of diol **4** with 2.5 equivalents of NMO and 5 mol% TPAP at rt for 17 h afforded the lactones **6** and **7** in 15% yield and in a 4:1 ratio (Table 1, entry 1). The major compound isolated was furane **10** (30%) formed by elimination of water after initial oxidation to lactol **11** (Scheme 3).

Improved yields and selectivities were achieved when the initial temperature was below 0 °C and the reaction mixture gradually warmed to rt over a period of 17 h (entries 2 and 3). Increasing the amount of TPAP and longer reaction times produced the lactones **6** and **7** in *ca.* 50% yield but the



Scheme 1



Scheme 2

Table 1 Reaction conditions for the TPAP-catalysed oxidation of diol **5** to lactones **6** and **7**

Entry	TPAP/mol%	*T*/°C	*t*/h	Yield (%)	Ratio **6**:**7**[a]
1	5	23	17	15	3,7:1
2	5	−30 → 23	17	21	22:1
3	5	−78 → 23	17	32	22:1
4	7,5	−78 → 23	62	47	**25**:**1**
5	10	−78 → 23	62	49	20:1
6	7,5 + 2,5 +2,5	−78 → 23	62	**50**	5,4:1

[a] Estimated by ^{1}H NMR spectra of crude reaction products.

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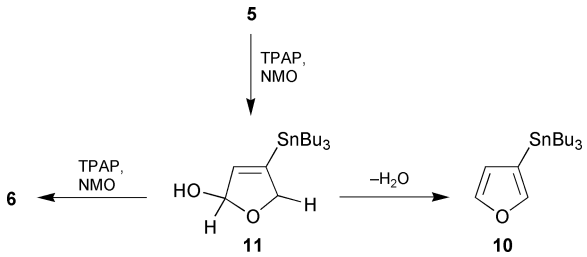


Scheme 3

selectivity decreased with higher contents of the oxidation reagent (entries 4–6).

Lactones **6** and **7** were inseparable by flash chromatography and were therefore used as a mixture for the Stille coupling. This reaction was performed with benzyl bromides **8a**–**h** as described previously.[9] The α,β-unsaturated lactones **9a**–**h** were isolated as isomerically pure compounds (Scheme 2). Sweeney *et al.* described recently, that the reaction rates for the Stille coupling of lactones **6** and **7** with aryl halides are different.[15] In analogy, only lactone **6** reacted with benzyl bromides **8a**–**h** to the coupling products **9a**–**h** (Table 2).

Table 2 Benzyl bromides **8a**–**h** employed for the Stille coupling and yields of the reaction products **9a**–**h**

Entry	Residue (R)	Bromide	Lactone	Yield (%)
1	4-Mesyl-3-methoxy	**8a**	**9a**	80
2	3,4,5-Trimethoxy	**8b**	**9b**	56
3	4-Methyl	**8c**	**9c**	76
4	H	**8d**	**9d**	70
5	4-Nitro	**8e**	**9e**	24
6	2,4,6-Trimethyl	**8f**	**9f**	77
7	3-Methoxy	**8g**	**9g**	59
8	3,4-Methylendioxy	**8h**	**9h**	45

Hydrogenation of lactones **9a**–**h** to lactones **2a**–**h** were achieved by means of 10% Pd on charcoal or Ra-Ni T4 (Table 3). The former catalyst, however, gave irreproducible results or no conversion. Additionally, high pressure (100 bar) and long reaction times (> 24 h) were required. With Ra-Ni T4 as catalyst, complete conversion was found in all cases within 2 h at 0.1 bar positive pressure.

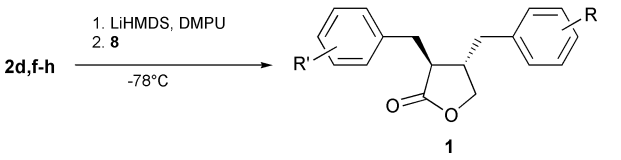
Table 3 Hydrogenation of the unsaturated lactones **9a**–**h** using different catalysts

Entry	Unsat. lactone	Product	Catalyst	*p*/bar	*t*/h	Yield (%)
1	**9a**	**2a**	Pd/C	0.1	14	93
2	**9a**	**2a**	Ra-Ni T4	0.1	2	98
3	**9b**	**2b**	Pd/C	0.1	14	0
4	**9b**	**2b**	Ra-Ni T4	0.1	2	70
5	**9c**	**2c**	Pd/C	0.1	24	98
6	**9d**	**2d**	Pd/C	50	48	97
7	**9e**	**2e**	Pd/C	0.1	14	0
8	**9f**	**2f**	Pd/C	0.1	14	0
9	**9f**	**2f**	Pd/C	100	72	88
10	**9f**	**2f**	Ra-Ni T4	0.1	2	98
11	**9g**	**2g**	Pd/C	100	14	92
12	**9h**	**2h**	$Pd(OH)_2$	100	16	0
13	**9h**	**2h**	Ra-Ni T4	0.1	2	70

Alkylation of lactones **2** with benzyl halides using LDA as base and HMPA as cosolvent provides lactone lignans **1**.[1,7,16] We found that alkylation using LHMDS as base and DMPU[17] as non-carcinogenic substitute for HMPA afforded lactones **1** in moderate yields (Scheme 4 and Table 4).

Bioassay of the synthetic lignan analogues using colon-tumor lines HT29 revealed that compound **1f** possesses high cytotoxic activity (IC_{50} = 40 mM).[18]

We have shown that β-benzyl-γ-butyrolactones **2** were effectively synthesised from butynediol **4** in four transition



Scheme 4

Table 4 Alkylation of lactones **2d**,**f**–**h** to the symmetrically and unsymmetrically substituted lignan analogues **1**

Entry	Lactone	Bromide	Residue (R′)	Lignan	Yield (%)[a]
1	**2d**	**8d**	H	**1d**	30
2	**2f**	**8f**	2,4,6-Trimethyl	**1f**	43
3	**2f**	**8h**	3,4-Methylendioxy	**1fb**	25
4	**2g**	**8g**	3-Methoxy	**1g**	18
5	**2h**	**8h**	3,4-Methylendioxy	**1h**	35

[a] Reaction conditions not optimized.

metal catalysed reactions. Alkylation of these compounds produced lignan analogues **1** with cytotoxic activities. An enantioselective route to this class of lignans is in progress.

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Notes and references

1 D. C. Ayres and J. D. Loike, *Lignans: Chemical, Biological and Clinical Properties*, Cambridge University Press, Cambridge, 1990; R. S. Ward, *Nat. Prod. Rep.*, 1999, **16**, 75.
2 Recent reviews: J. L. Charlton, *J. Nat. Prod.*, 1998, **61**, 1447; E. Eich, *ACS Symp. Ser.*, 1998, **691**, 83; A. J. Vlietinck, T. De Bruyne, S. Apers and L. A. Pieters, *Planta Med.*, 1998, **64**, 97.
3 Recent reviews: S. E. Rickard and L. U. Thompson, *ACS Symp. Ser.*, 1997, **662**, 273; D. M. Tham, C. D. Gardner and W. L. Haskell, *J. Clin. Endocrinol. Metab.*, 1998, **83**, 2223; C. D. N. Humfrey, *Nat. Toxins*, 1998, **6**, 51; J. M. Cline and C. L. Hughes, Jr., *Cancer Treat. Res.*, 1998, **94**, 107; W. Mazur and H. Adlercreutz, *Pure Appl. Chem.*, 1998, **70**, 1759; S. Bingham, *Pure Appl. Chem.*, 1998, **70**, 1777.
4 S. R. Stitch, J. K. Toumba, M. B. Groen, C. W. Funke, J. Leemhuis, J. Vink and G. F. Woods, *Nature*, 1980, **287**, 738; K. D. R. Setchell, A. M. Lawson, F. L. Mitchell, H. Adlercreutz, D. N. Kirk and M. Axelson, *Nature*, 1980, **287**, 740; M. Axelson, J. Sjövall, B. E. Gustafsson and K. D. R. Setchell, *Nature*, 1982, **298**, 659; L. U. Thompson, P. Robb, M. Serraino and F. Cheung, *Nutr. Cancer*, 1991, **16**, 43.
5 R. S. Ward, *Chem. Soc. Rev.*, 1982, **11**, 75; R. S. Ward, *Tetrahedron*, 1990, **46**, 5029.
6 N. J. Cartwright and R. D. Haworth, *J. Chem. Soc.*, 1944, 535; K. Weinges and R. Spänig, in *Oxidative Coupling of Phenols*, ed. W. I. Taylor and A. R. Battersby, Marcel Dekker, New York, 1967; D. E. Bogucki and J. L. Charlton, 1997, **75**, 1793.
7 J. M. de L. Vanderlei, F. Coelho and W. P. Almeida, *Synth. Commun.*, 1998, **28**, 3047.
8 J. K. Stille, *Angew. Chem.*, 1986, **98**, 504; V. Farina, V. Krishnamurthy and W. J. Scott, *Org. React.*, 1997, **50**, 512.
9 S. Kamlage, M. Sefkow and M. G. Peter, *J. Org. Chem.*, 1999, **64**, 2938.
10 H. X. Zhang, F. Guibe and G. Balavoine, *J. Org. Chem.*, 1990, **55**, 1857.
11 A. G. M. Barrett, T. E. Barta and J. A. Flygare, *J. Org. Chem.*, 1989, **54**, 4246.
12 G. J. Hollingworth, G. Perkins and J. Sweeney, *J. Chem. Soc., Perkin Trans. 1*, 1996, 1913.
13 S. V. Ley, J. Norman, W. P. Griffith and S. P. Marsden, *Synthesis*, 1994, 639–666.
14 R. Bloch and C. Brillet, *Synlett*, 1991, 829.
15 R. Mabon, A. M. E. Richecœur and J. B. Sweeney, *J. Org. Chem.*, 1999, **64**, 328.
16 R. Chênevert, G. Mohammadi-Zirani, D. Caron and M. Dasser, *Can. J. Chem.*, 1999, **77**, 223.
17 T. Mukhopadhyay and D. Seebach, *Helv. Chim. Acta*, 1982, **65**, 385.
18 T. W. Becker, M. G. Peter and B. L. Pool-Zobel, in *Proceedings of the Food and Cancer Prevention III Meeting, Norwich, UK*, 1999, ed. I. T. Johnson and G. R. Fenwick, Special Publication No 255, Royal Society of Chemistry, Cambridge, UK, p. 151.