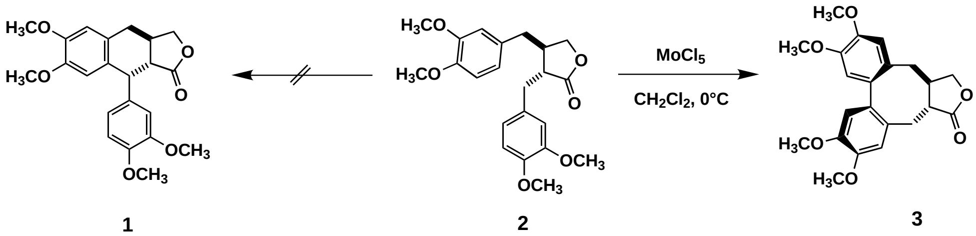
Highly Selective Formation of Eight-Membered-Ring Systems by Oxidative Cyclization with Molybdenum Pentachloride—An Environmentally Friendly and Inexpensive Access to 2,2′-Cyclolignans**

Beate Kramer, Anne Averhoff, and
Siegfried R. Waldvogel*

Dedicated to Professor Hans J. Schäfer
on the occasion of his 65th birthday

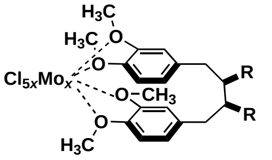
The tetramethoxybiaryl moiety is a common unit in natural products.[1] Because of their high biological activities eight-membered-ring lignans (2,2′-cyclolignans), which contain this structural unit, are of particular interest.[2] The key step in lignan synthesis is often an oxidative biaryl coupling reaction in which the axial chirality is determined by the stereochemical information in the backbone of the precursor. In the oxidative cyclization reaction, most transition-metal reagents and hypervalent-iodine derivatives give mixtures of the desired eight-membered-ring compounds (2,2′-cyclolignans) and of six-membered-ring derivatives (2,7′-cyclolignans).[3] Of particular interest for the non-phenolic oxidative coupling reaction is the dehydrodimerization of the natural product (−)-dimethylmatairesinol (**2**) to (+)-5-detigloyloxysteganolid (**3**; Scheme 1).



Scheme 1. Undesired six-membered-ring formation (→**1**) and desired eight-membered-ring formation (→**3**) upon oxidative coupling of (−)-dimethylmatairesinol (**2**).

Excellent selectivities favoring the 2,2′-cyclolignans are obtained with the highly toxic thallium(III) reagents or complex reaction mixtures, which require a combination of solvents and strong Lewis acids.[4] We report herein an efficient and highly selective formation of 2,2′-cyclolignans which employs molybdenum pentachloride as the sole reagent. Molybdenum pentachloride is a widely available and inexpensive reagent that can be exploited for the oxidative coupling reaction of electron-rich arenes.[5] The resulting metal waste is easily removed from the reaction mixture and can be recovered.[6]

The (−)-dimethylmatairesinol (**2**), which is required for the cyclization, was synthesized according to the method of Pelter et al.[7] The conversion with molybdenum pentachloride proceeded without problems; even a high concentration of starting material resulted in 50 % yield of the desired 2,2′-cyclolignan.[8] The six-membered-ring compound was not detected in the reaction mixture. The other components obtained were unreacted starting material **2** and oligomeric products. The present reaction is the first application of molybdenum pentachloride as an oxidant in the total synthesis of natural products. Similar to the thallium-mediated coupling reaction, the high selectivity for the eight-membered lignans and the lack of benzylic coupling might be explained by the formation of a complex that involves the oxophilic Lewis acid (Scheme 2).



Scheme 2. Complexation of the molybdenum center through the methoxy oxygen atoms

In the oxidative coupling reaction, molybdenum pentachloride favors substrates with a 1,2-dialkoxy substitution pattern. Most likely, the reaction is initiated by an electron transfer from a benzene moiety to the molybdenum fragment. A subsequent intramolecular electrophilic cyclization and rearomatization sequence affords the product.[9] Since the substrate **2** contains many oxygen atoms to coordinate the reagent, we reasoned that two or more clustered molybdenum centers are involved. To gain support for such an intermediate (Scheme 2), we synthesized two further 1,4-bis(3,4-dimethoxyphenyl)butanes **4a** and **4b**[10] and subjected both to the cyclization reaction. The key step in the stereoselective construction of **4b** is the nickel-catalyzed Grignard coupling reaction of the *meso*-1,4-diiodo-2,3-dimethylbutane, which is readily made from *meso*-2,3-dimethylsuccinic acid.[10] The spatial arrangement of both substituents in the butanediyl bridge of the intermediate, the conversion into **5b** should be disfavored [Eq. (1)].

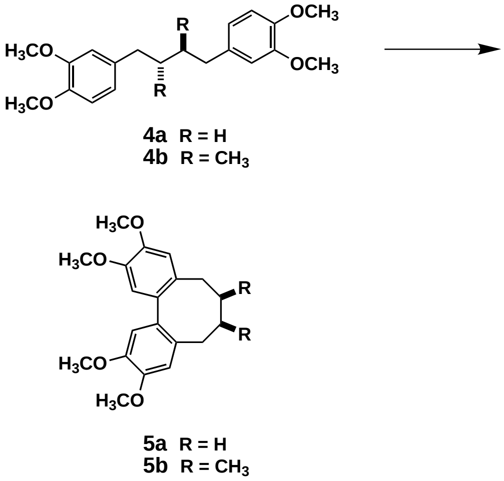
Compound **4a** was already converted at ice-bath temperature and high concentration into **5a** (76 % yield). In contrast, reflux conditions and high dilution were required for the successful synthesis of **5b**.[11] Besides the desired lignan **5b** (30 % yield), we recovered mainly unreacted starting material. In both conversions the only cyclization products are the 2,2′-cyclolignans **5**.

In conclusion, eight-membered-ring systems, which are of particular interest for the total synthesis of 2,2′-cyclolignans, are exclusively formed when using molybdenum pentachloride as the oxidant. Harsher reaction conditions are required for the synthesis because of unfavorable steric interactions in

---

[*] Dr. S. R. Waldvogel, B. Kramer, A. Averhoff
Organisch-Chemisches Institut
Westfälische Wilhelms-Universität Münster
Corrensstrasse 40, 48149 Münster (Germany)
Fax: (+49) 251-83-39772
E-mail: waldvog@uni-muenster.de

[**] The work was supported by the Deutschen Forschungsgemeinschaft and H. C. Starck (Goslar, Germany) by a donation of $MoCl_5$. We particularly thank Prof. Dr. Dieter Hoppe for fruitful discussions and support in this project.



(1)

the butanediyl moiety. Molybdenum pentachloride is an environment-friendly alternative to the highly toxic thallium(III) reagents. Furthermore, no additional Lewis acids are required. We are currently investigating the application of this powerful reagent to the synthesis of other natural products.

Received: March 28, 2002 [Z19007]

---

[1] G. Bringmann, R. Walter, R. Weirich, *Angew. Chem.* **1990**, *102*, 106–119; *Angew. Chem. Int. Ed. Engl.* **1990**, *29*, 977–990.

[2] L. G. Monovich, Y. Le Huérou, M. Rönn, G. A. Molander, *J. Am. Chem. Soc.* **2000**, *122*, 52–57, and references therein.

[3] R. Venkateswarlu, C. Kamakshi, S. G. A. Moinuddin, P. V. Subhash, R. S. Ward, A. Pelter, S. J. Coles, M. B. Hursthouse, M. E. Light, *Tetrahedron* **2001**, *57*, 5625–5632; R. C. Cambie, G. R. Clark, P. A. Craw, P. S. Rutledge, P. D. Woodgate, *Aust. J. Chem.* **1984**, *37*, 1775–1784; E. C. Taylor, J. G. Andrade; G. J. H. Rall, A. McKillop, *J. Am. Chem. Soc.* **1980**, *102*, 6513–6519.

[4] J. S. Buckleton, R. C. Cambie, G. R. Clark, P. A. Craw, C. E. F. Rickard, P. S. Rutledge, P. D. Woodgate, *Aust. J. Chem.* **1988**, *41*, 305–324; H. Hamamoto, G. Anilkumar, H. Tohma, Y. Kita, *Chem. Commun.* **2002**, 450–451.

[5] S. R. Waldvogel, R. Fröhlich, C. A. Schalley, *Angew. Chem.* **2000**, 112, 2580–2583; *Angew. Chem. Int. Ed.* **2000**, *39*, 2472–2475; S. R. Waldvogel, A. R. Wartini, P. H. Rasmussen, J. Rebek, Jr., *Tetrahedron Lett.* **1999**, *40*, 3515–3517; S. Kumar, M. Manickam, *Chem. Commun.* **1997**, 1616–1617.

[6] The reaction mixtures were fractionated with ethyl acetate and water. The aqueous solutions were neutralized. After several days, the molybdates precipitated and were filtered off.

[7] A. Pelter, R. S. Ward, D. M. Jones, P. Maddocks, *J. Chem. Soc. Perkin Trans. 1* **1993**, 2631–2637.

[8] **3**: Conversion of **2** in CH_2Cl_2 (70 mM) with $MoCl_5$ (2 equiv) at 0 °C for 50 min, followed by purification by column chromatography gave **3** as colorless crystals. All analytical data (m.p. 121 °C, ^{1}H and ^{13}C NMR, MS) match those of Ref. [4]; elemental analysis (%): calcd for $C_{22}H_{24}O_6$ (384.2): C 68.77, H 6.25; found: C 68.75, H 6.39; $[\alpha]_D^{24} = +161.5°$.

[9] S. R. Waldvogel, *Synlett* **2002**, 622–624.

[10] **4a**: G. Traverso, *Gazz. Chim. Ital.* **1959**, *89*, 1818–1823; **4b**: *meso*-1,4-diiodo-2,3-dimethylbutane analogous to W. Schlenk, Jr., *Liebigs Ann. Chem.* **1973**, 1195–1209. Treatment with 3,4-dimethoxyphenylmagnesium iodide (20 equiv) in THF with addition of 1,1′-bis(diphenylphosphanyl)ferrocenenickel(II) chloride. After 4 days at ambient conditions the product was isolated in 60 % yield in an analytically pure form which was identical to known compound (see **5b**).

[11] **5a**: Synthesis analogous to **3**, analytical data differ significantly from: A. Ronlan, V. D. Parker, *J. Org. Chem.* **1974**, *39*, 1014–1016: m.p. 121 °C; ^{1}H NMR (600 MHz, $CDCl_3$, 25 °C, TMS): $\delta = 1.45$ (dd, $^3J(H,H) = 9$ Hz, $^3J(H,H) = 9$ Hz, 2H; 5-H_{ax}), 2.05 (dd, $^3J(H,H) = 9$ Hz, $^3J(H,H) = 11$ Hz, 2H; 6-H_{ax}), 2.11 (dd, $^3J(H,H) = 11$ Hz, $^3J(H,H) = 13$ Hz, 2H; 6-H_{aq}), 2.64 (dd, $^3J(H,H) = 9$ Hz, $^3J(H,H) = 13$ Hz, 2H; 5-H_{aq}), 3.88 (s, 6H; OCH_3), 3.91 (s, 6H; OCH_3), 6.75 ppm (s, 4H; H_{ar}); ^{13}C NMR (100.5 MHz, $CDCl_3$, 25 °C, TMS): $\delta = 29.42$, 32.50, 55.96, 55.98, 112.28, 132.56, 135.07, 146.74, 148.55 ppm; elemental analysis (%): calcd for $C_{20}H_{24}O_4$ (328.4): C 73.15 , H 7.37; found: C 72.91, H 7.37. **5b**: A solution (0.5 mM) of **4b** in CH_2Cl_2 was treated with $MoCl_5$ (2 equiv) and heated at reflux for 2 h. After workup and purification by column chromatography **5b** was isolated in 30 % yield; analytical data were identical with those reported in the literature: R. Dhal, Y. Landais, A. Lebrun, V. Lenain, J.-P. Robin, *Tetrahedron* **1994**, *50*, 1153–1164. Furthermore, **4b** was recovered (52 %).