Tetrahedron Letters, Vol.27, No.2, pp 127-130, 1986 0040-4039/86 $3.00 + .00
Printed in Great Britain

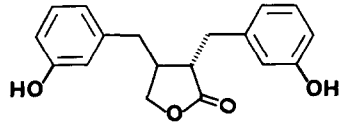
OXIDATIVE COUPLING. II. THE TOTAL SYNTHESIS OF ENTEROLACTONE

J. L. Belletire*, S. L. Fremont
Department of Chemistry
University of Cincinnati
Cincinnati, Ohio 45221

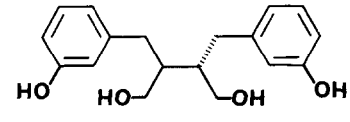
Abstract: Oxidative coupling of 3-methoxyhydrocinnamic acid dianion with molecular iodine forms the key step in an efficient synthesis of enterolactone.

In 1980 investigators reported (1) the isolation of two unusual urinary metabolites. Enterolactone 1 and enterodiol 2, both secreted by the normal flora of intestinal bacteria (2), are the first naturally occurring lignans to be found in humans. The intriguing endocrine-coupled pattern of enterolactone production (3) and the significant biological activity of enterolactone (4) have generated intense interest in this compound.

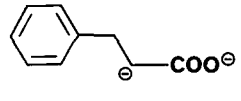
Kirk et al. recently published (5) a detailed analysis of the crystallographic and spectroscopic properties of enterolactone. Among several reported syntheses of enterolactone are those by Kirk (6), Groen (7), Snieckus (8), and Pelter (9).



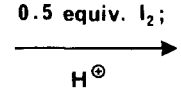
1

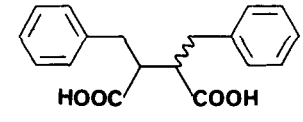


2



3





4

In our initial examination of carboxylic acid dianion oxidative coupling (10), it was noted that hydrocinnamic acid dianion **3** produces **4** in 77% yield. That **4** possesses the basic lignan carbon skeleton (11) suggested the possible utility of oxidative coupling in a general synthetic approach to lignans. The overall skeletal and substitution pattern in **1** is well-suited to such a dimerization sequence. The remaining synthetic obstacles (control of the oxidation level to afford a lactonic product and adjustment of the stereochemistry about the lactone ring) are easily solved.

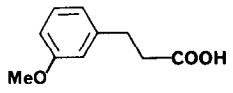
Commercially available m-methoxycinnamic acid undergoes smooth hydrogenation (H_2 (1 atm), 10% Pd(C), EtOAc; distilled yield 99%) to provide crystalline **5** (m.p. 43.5-45°C).

Conditions for optimal generation of dianion intermediate **6** were explored through a series of model alkylations involving the addition of 1.0 equivalent of CH_3I. Maximum dianion concentration occurs upon addition of **5** to 2.0 equivalents of LDA in THF at -78°C followed by stirring at -78°C to 0°C over 2.5 hrs. and then 5.0 hrs. at 0°C. Higher temperatures, which led to intensely colored solutions, were detrimental.

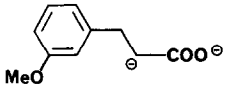
Oxidative coupling of **6** is achieved by cooling the dianion solution (~0.15M) to -60°C and then adding over 2.0 minutes 0.5 equivalents of molecular iodine in THF (~0.4M). The resulting pale yellow solution is stirred at RT for 12 hrs., the THF is removed on a rotary evaporator, 12N HCl and $CHCl_3$ are added to the residue, and the layers are partitioned. The organic phase is washed with saturated $NaHSO_3$ solution and then extracted with 2N KOH. The aqueous base layer is acidified followed by back-extraction with EtOAc. NMR analysis of the crude reaction mixture reveals that **7** is formed in ca. 85% yield. Simple recrystallization from CH_3OH affords a 63% isolated yield of **7**. Although the remaining mother liquors contain additional **7** (which can be recovered via flash chromatography), the direct recrystallization procedure is particularly convenient. Comparable percentage yields of **7** are obtained over a range employing 3-12 mmoles of **5**. In spite of a narrow melting point range (172.5-173.5°C), the recrystallized product is a mixture of stereoisomers. Examination of the ^1H nmr in the methoxy region indicates a ca. 4.5:1 isomer ratio. By analogy to earlier results (10), the predominant isomer is tentatively assigned as threo.

Upon treatment of **7** with excess acetic anhydride at reflux for 48 hrs., anhydride **8** forms in quantitative yield. Careful ^{13}C nmr reveals that this material is a single stereoisomer (12). In practice the crude acetic anhydride reaction mixture is carefully treated with excess CH_3OH and then held at reflux for an additional 48 hrs. This results in smooth conversion to acid ester **9**. To a solution of **9** in Et_2O is added $BH_3{\cdot}SMe_2$ (8.0 equivalents; -20°C for 30 minutes; 0° for 3 hrs.). Acidification and the usual workup affords hydroxymethyl derivative **10**, which, upon overnight pumping to remove the last traces of solvent, is smoothly transformed into lactone dimethyl ether **11**, a viscous, colorless oil. The only required purification after recrystallization of **7** is a flash chromatography of **11**. The overall yield from **7** to chromatographed **11** is 89%.

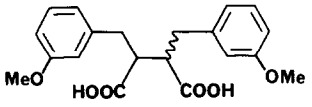
Demethylation of **11** is accomplished with BBr_3 (1.9 equivalents; CH_2Cl_2; -78°C to -40°C over 1.25 hrs., then 0°C for 4.0 hrs.; R.T. for 3.75 hrs.). Upon workup, spectroscopically pure **1** is isolated as a colorless syrup (chromatographed yield from **11** to **1**: 90%). Initially, crystallization of **1** is difficult (13). After prolonged trituration with ligroine, spontaneous crystallization does occur. Recrystallization from EtOAc-ligroine or CH_2Cl_2-CH_3OH gives dense rhombs. A mixed melting point with authentic enterolactone is undepressed while our spectral data are in complete accord with published values.



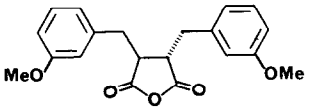
5



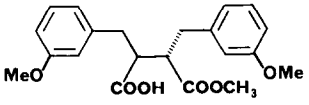
6



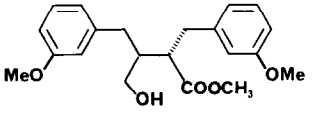
7



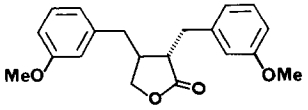
8



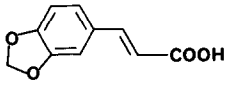
9



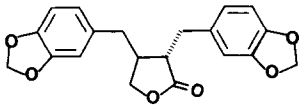
10



11



12



13

Since enterolactone **1** is easily converted into enterodiol **2** (6,7,8), this work also constitutes a formal total synthesis of enterodiol.

To explore the scope of this approach we have carried out preliminary experiments involving a similar sequence commencing with commercially available **12** and leading to material whose ^{1}H nmr, ^{13}C nmr, ir, and high resolution m/e are consistent with hinokinin **13** (14).

Further applications of this oxidative coupling technique to more complex lignan natural products are underway.

Acknowledgements

We would like to thank the Lalor Foundation, the Eppley Foundation, the Research Corporation, and the URC of the University of Cincinnati for their generous financial support. High resolution nmr and mass spectroscopy studies were performed on instruments purchased through National Science Foundation grants CHE-8102974 and PCM-8219912, respectively. The authors also thank Drs. Snieckus and Groen for having supplied us with authentic samples of enterolactone.

References and Notes

1. (a) Stitch, S. R.; Toumba, J. K.; Groen, M. B.; Funke, C. W.; Leemhuis, J.; Vink, J.; Woods, G. F. Nature (London) **1980**, 287, 738. (b) Setchell, K.D.R.,; Lawson, A. M.; Mitchell, F. L.; Adlercreutz, H.; Kirk, D. N.; Axelson, M. Ibid. **1980**, 287, 740.
2. (a) Setchell, K.D.R.; Borriello, S. P.; Gordon, H.; Lawson, A. M.; Harkness, R.; Morgan, D.M.L.; Kirk, D. N.; Adlercreutz, H.; Anderson, L. C.; Axelson, M. Lancet **1981**, ii, 4. (b) Axelson, M.; Sjovall, J.; Gustaffson, B. E.; Setchell, K.D.R. Nature (London) **1982**, 298, 659.
3. Setchell, K.D.R.; Lawson, A. M.; Axelson, M.; Adlercreutz, H. Res. Steroids **1981**, 9, 207.
4. Walters, A. P.; Knowler, J. T. J. Reprod. Fertil. **1982**, 66, 379.
5. Cooley, G.; Farrant, R. D.; Kirk, D. N.; Patel, S.; Wynn, S.; Buckingham, M. J.; Hawkes, G. E.; Hursthouse, M. B.; Galas, A.M.R.; Lawson, A. M.; Setchell, K.D.R. J. Chem. Soc. Perkin Trans. 2 **1984**, 489.
6. Cooley, G.; Farrant, R. D.; Kirk, D. N.; Wynn, S. Tetrahedron Lett. **1981**, 21, 349.
7. Groen, M. B.; Leemhuis, J. Tetrahedron Lett. **1980**, 21, 5043.
8. Mahalanbis, K. K.; Mumtaz, M.; Snieckus, V. Tetrahedron Lett. **1982**, 23, 3975.
9. (a) Pelter, A.; Satyanarayana, P.; Ward, R. S. Tetrahedron Lett. **1981**, 22, 1549.
   (b) Kirk, D. N.; McLaughlin, L. M.; Lawson, A. M.; Setchell,, K.D.R.; Patel, S. K. J. Chem. Soc. Perkin Trans. 1 **1985**, 35.
10. Belletire, J. L.; Spletzer, E. G.; Pinhas, A. R. Tetrahedron Lett. **1984**, 25, 5969.
11. Rao, C.B.S. "Chemistry of Lignans", Andhra University Press, Waltair, 1978.
12. Hussain, S.A.M.T.; Ollis, W. D.; Smith, C.; Stoddart, J. F. J. Chem. Soc. Perkin Trans. 1, **1975**, 1480.
13. This problem was also noticed by M. B. Groen, private communication, 1985.
14. (a) Asana, Y.; Kamikawa, T.; Tokoroyama, T. Bull. Chem. Soc. Jpn. **1976**, 49, 3232 (1976).
    (b) Haworth, R. D.; Woodcock, D. J. Chem. Soc. **1938**, 1985.
    (c) Haworth, R. D.; Wilson, L. J. Chem. Soc. **1950**, 71.

(Received in USA 16 September 1985)