Novel Oxidative Transformation of Indenoisoquinolines to Isoquinoline-3-spiro-3′-phthalides in the Presence of Osmium Tetraoxide and 4-Methylmorpholine *N*-Oxide

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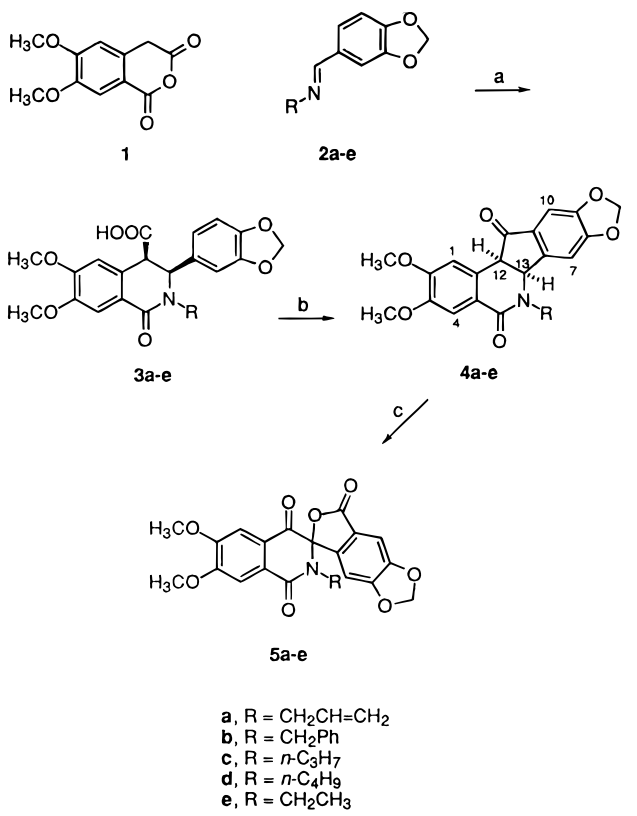
Osmium-mediated dihydroxylation of olefins has proven to be extremely valuable in organic synthesis.[1] Although the use of stoichiometric osmium presents major drawbacks in terms of both toxicity and cost, the Sharpless asymmetric dihydroxylation reaction permits enantioselective reactions utilizing catalytic amounts of osmium and has been utilized extensively in various total syntheses.[2,3] In the case of catalytic dihydroxylation, the catalytic cycle may be viewed in three stages: (1) osmylation, i.e., alkene oxidation by Os^{VIII}; (2) hydrolysis of the Os^{VI} osmate ester; and (3) reoxidation of osmium by a terminal oxidant. The "Upjohn procedure" employing 4-methylmorpholine *N*-oxide (NMO) has widely been used for step 3.[4] Despite the wide utility of these reactions and extensive research, the mechanism of this reaction is still obscure and a matter of debate.[5,6]

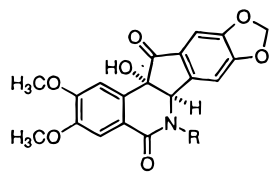
In the course of our work on the synthesis of analogues of indenoisoquinolines,[7] which were identified as highly cytotoxic topoisomerase I inhibitors and are currently under biological evaluation,[8] we attempted the osmium-catalyzed dihydroxylation of the double bond of the allyl group in the indenoisoquinoline **4a** (Scheme 1). Osmium tetraoxide (2 drops, 2.5% solution in *t*-BuOH) was added at 0 °C to a solution of the allyl compound **4a** (1 mmol) and NMO (2 mmol) in CH_2Cl_2/*t*-BuOH/H_2O (5 mL/13 mL/10 mL), and the reaction mixture was stirred overnight. After column purification, a less polar compound than the starting material was isolated in 60% yield. Unexpectedly, the ^{1}H NMR spectrum of the product revealed an intact *N*-allyl group and the disappearance of the two methine protons that had been present at C-12 and C-13 in the starting material. The IR spectrum of the product displayed a strong carbonyl absorption at 1776 cm^{-1} as well as two other bands at 1689 and 1657 cm^{-1} that were assumed to indicate the presence of two additional carbonyl groups. On the basis of analytical and spectral data, the product was assigned the spirolactone structure **5a** (Scheme 1). Under similar conditions, the indenoisoquinolines **4b**−**e** afforded isoquinoline-3-spiro-3′-phthalides **5b**−**e**. The structure of **5b** was confirmed by a single-crystal X-ray diffraction analysis.

Scheme 1[a]

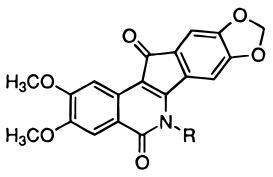


[a] Reagents and conditions: (a) $CHCl_3$, rt (30 min); (b) Eaton's reagent, rt (6−12 h); (c) OsO_4, NMO, *t*-BuOH, H_2O, 0−23 °C (10 h).

In all of the reactions, the starting indenoisoquinolines **4a**−**e** were completely consumed. The yields of the isoquinoline-3-spiro-3′-phthalides isolated after column chromatography were **5a** (60%), **5b** (92%), **5c** (88%), **5d** (81%), and **5e** (92%). In each case, minor amounts of a polar coproduct were detected in addition to the isoquinoline-3-spiro-3′-phthalides. When the indenoisoquinolines **4b** and **4c** were subjected to the reaction conditions at room temperature instead of at 0 °C, the polar coproducts formed in greater amounts. The structures **6b** and **6c** were assigned to these more polar products on the basis of the spectral and the analytical data. The assigned structure **6b** was further confirmed by single-crystal X-ray diffraction analysis. In the case of **4b**, the products **5b** and **6b** were obtained in a ratio of 7:3, respectively, in 95% total yield. In the case of **4c**, the ratio of **5c** to **6c** was found to be 68:32, respectively. In general, it was found that the relative amounts of the hydroxylation products **6** could be increased by adding more dichloromethane to the reaction mixtures.



6b, R = CH_2Ph
6c, R = *n*-C_3H_7



7b, R = CH_2Ph
7e, R = CH_2CH_3

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The hydroxylated products **6b** and **6c** were subjected to the reaction conditions in order to investigate the possible roles of the C-12 hydroxylated indenoisoquinolines as intermediates in the transformation of **4** to **5**. The results showed clearly that **6b** and **6c** were not converted to **5b** and **5c**. In addition, it was determined that the reaction does not take place in the absence of osmium tetraoxide and that treatment of the indenoisoquinoline **4** with 1 equiv of osmium tetraoxide without NMO also does not effect any reaction. Hypothetical intermediates **7b** and **7e** were obtained by thionyl chloride oxidation of **4b** and **4e**.[7] Both **7b** and **7e** were recovered unchanged even after subjection to the osmium tetraoxide−NMO reaction conditions for 2 days, indicating that they could not possibly be intermediates in the conversion of indenoisoquinolines **4** to isoquinoline-3-spiro-3′-phthalides **5**.

In conclusion, the transformation of indenoisoquinolines **4** to isoquinoline-3-spiro-3′-phthalides **5** is unusual and cannot be rationalized easily by "traditional" alkene osmylation chemistry. Further studies are currently underway to probe the scope and mechanism of this novel oxidative transformation.

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Supporting Information Available: Experimental procedures and spectroscopic data for all compounds, as well as ORTEP drawings and X-ray data in support of structures **5b** and **6b** (42 pages).

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