Pergamon

Tetrahedron Letters 40 (1999) 1771–1774

TETRAHEDRON
LETTERS

Palladium (II) catalyzed regioselective lactonization of steroids. Chemoselective construction of novel estrone derivatives

L. Troisi[a], G. Vasapollo[b], B. El Ali[c], G. Mele[b], S. Florio[d], V. Capriati[d]

a) Dipartimento diBiologia, Università diLecce, Via Monteroni, I-73100-Lecce, Italy; b) Facoltà diIngegneria, Università di Lecce, Via Monteroni, I-73100 Lecce, Italy; c) Chemistry Department, King Fahd University of Petroleum & Minerals, 31261 Dhahran, Saudi Arabia; d) C.N.R., Centro di Studio sulle Metodologie Innovative divSintesi Organiche, Dipartimento Farmaco-Chimico, Università di Bari, Via E.Orabona 4, I-70125 Bari, Italy

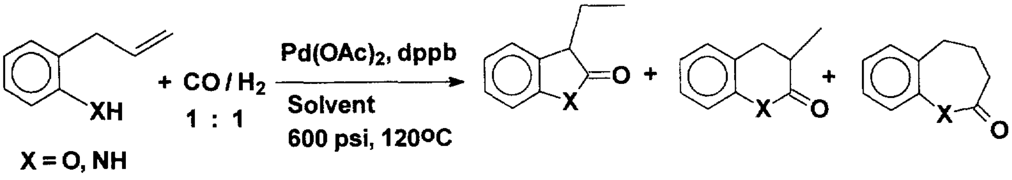
Received 15 July 1998; revised 4 January 1999; accepted 7 January 1999

Abstract: Palladium acetate and 1,4-bis(diphenylphosphino)butane (dppb) catalyze regioselective cyclocarbonylation of 4-allylsteroids forming exclusively 7-membered ring lactones with excellent yields (96-98 %). The stereoselective addition of an epoxide ring on the side-chain of steroids is realized by coupling the carbonyl group of the cyclopentanone ring of the steroid with 2-benzothiazolylchloromethyllithium **1** or 4,4-dimethyl-2-oxazolinylchloroalkylithiums **2** and **3**.

Keywords: Palladium; Lactones; Epoxides; Steroids

Steroids are a biologically important class of compounds and they have a large range of applications in the pharmaceutical industry.[1, 2] Interesting methods of functionalization of steroids have been described.[3-5] Estrones represent an important type of aromatic steroid and exhibit a large spectrum of biological activity.[1, 3, 4] The structural features of new estrone derivatives having lactone and epoxide rings may play a critical role in increasing the biological activities of steroids, and in building new active pharmaceuticals. Intramolecular transition metal–catalyzed cyclocarbonylation of unsaturated alcohols and amines have been used extensively in the synthesis of heterocycles.[6, 7]

Recently, 5-, 6-, and 7-membered lactones fused to aromatic rings have been selectively obtained *via* palladium (II) and 1,4-bis(diphenylphosphino)butane (dppb) catalyzed intramolecular lactonization of 2-allylphenol and 2-allylaniline derivatives (eq.1).[8]

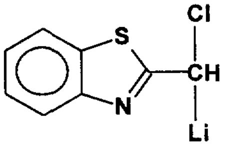


eq.1

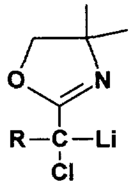
PII: S0040-4039(99)00094-5

Epoxides are widely recognized as important synthetic intermediates.[9, 10] Various methods of epoxidation have been described.[9] Methods for selective synthesis of oxiranes based on the coupling of carbonyl compounds with 2-benzothiazolylchloromethyllithium **1**, 2-oxazolinylchloroalkyllithiums **2** and **3** have been reported.[10]

In this communication, we wish to report the successful application of the intramolecular cyclocarbonylation and oxirane synthesis to the construction of new estrone derivatives containing both epoxide and 7-membered lactone rings. The lactonization reaction was catalyzed by the system $Pd(OAc)_2$-dppb in the presence of a 1:1 mixture of CO/H_2.[11] The epoxidation reaction was realized by coupling the carbonyl group of the cyclopentanone ring of estrone with 2-benzothiazolylchloromethyllithium **1**.[11]



1



2(R=H); **3**($R=CH_3$)

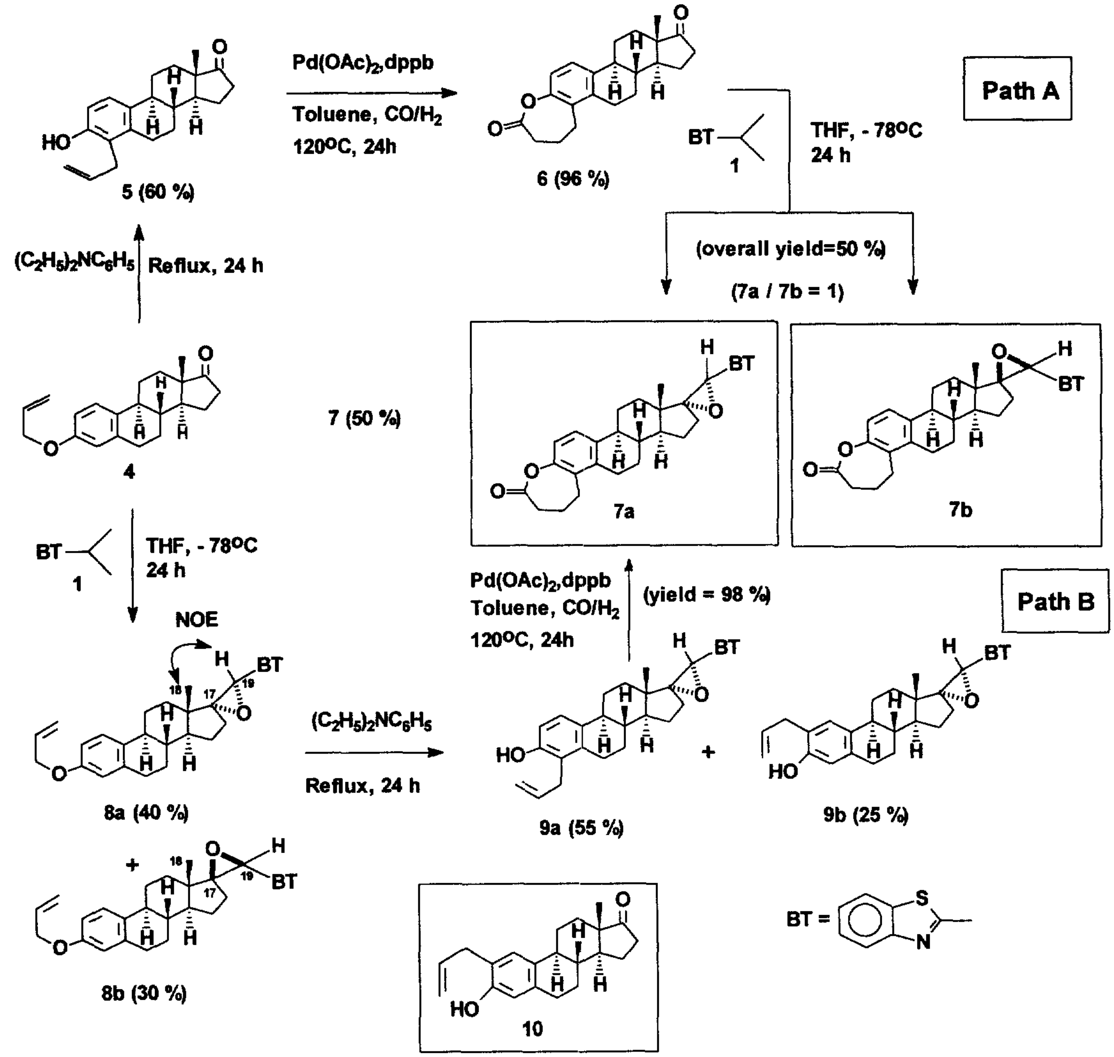
Two reaction schemes for the synthesis of the estrone derivative **7**, having a seven-membered ring lactone and an epoxide incorporated in its structure are described in Scheme 1.

According to path **A**, the Claisen rearrangement of estrone 3-allyl ether **4**[12] gives 4-allylestrone **5** in 60% yield (40% of the isomer **10** is also obtained).[13] The intramolecular cyclocarbonylation of **5** furnishes the 7-membered ring lactone-estrone **6** in 96% yield.[11] The coupling of the estrone derivative **6** with 2-benzothiazolylchloromethyllithium **1**[10, 11] leads to the epoxy-lactone-estrone derivative **7** (50% yield) as an inseparable mixture of **7a** and **7b** (the ratio of **7a**/**7b** = 1 was determined by ^{1}H-NMR). An alternative route for the synthesis of **7a** (path **B**, Scheme 1) involves the preliminary reaction of **4** with **1**. In this case the two isomers **8a** and **8b** formed could be isolated by column chromatography (silica gel, Et_2O/petroleum ether=7/3). The elucidation of their structures was achieved by means of their NOESY spectra and by comparing characteristic NMR signals with those of similar systems reported in the literature.[14] Claisen rearrangement of the o-allyl-epoxy-estrone derivative **8a** (55 %, Scheme 1) followed by cyclocarbonylation of the resulting 4-allylepoxyestrone derivative **9a** (25 % of the isomer **9b** was also formed) gave **7a** in 98 % yield. Both routes gave almost the same yields of lactonization (96-98%) and epoxidation (40-50%) reactions.

Analogous epoxy-lactones have been synthesized in the presence of the catalytic system $Pd(OAc)_2$-dppb-CO-H_2 and 2-benzothiazolylchloromethyllithium **1** or 4,4-dimethyl-2-oxazolinylchloroalkyllithiums **2** and **3**.

In conclusion, we have reported simple regioselective routes to new estrone derivatives having both epoxide and 7-membered lactone rings. Further work is in progress.

Scheme 1



Acknowledgements: This work was carried out in the framework of the National Project "Stereoselezione in Sintesi Organica. Metodologie ed Applicazioni" supported by the Ministero dell' Università e della Ricerca Scientifica e Tecnologica (MURST), Rome, and by the University of Bari and Lecce. The work was also carried out in the framework of the international collaboration between the Chemistry Department at KFUPM (Saudi Arabia) and the Faculty of Engineering at the University of Lecce. We thank the italian CNR (Rome) for financial support. Dr. B. El Ali thanks KFUPM (Saudi Arabia) for support.

REFERENCES AND NOTES:

1. Dence J. B. *Steroids and Peptides*, New York, Wiley-Interscience, **1980.**
2. Johns W. F. *MTP International Review of Science*, Vol. 8, Baltimore, Chemistry Park Press, **1973.**
3. a) Turner A. B. *Nat. Prod. Rep.* **1992**, 9, 37; **1991**, 8, 17; **1989**, 6, 539. b) Trost B. M., Kulawiec R. J., Mammes A. *Tetrahedron Lett.* **1993**, 34, 587.
4. Wilson S. R., Yasmin A. in "*Studies in Natural Products Chemistry*", Vol. 10, Atta-ur-Rehman, Ed. Elsevier, Amsterdam, **1992**, 43.
5. a) Radpatt J., Zeelen F. *J. Chem. Soc. Rev.* **1983,** 12, 75. b) Kametani T. *Actual. Chim. Theor.* **1988**, 15, 131.
6. El Ali B., Alper H. in "*Transition Metal Catalyzed Reactions*", by Davies SG and Murahashi SI.; London: Blackwells; **1999** (in press).
7. El Ali B., Alper H. in "*Transition Metal for Fine Chemicals and Organic Synthesis* ", by Bolm C. and Beller M.; Weinheim-Germany; VCH; **1998**.
8. El Ali B., Okuro K., Vasapollo G., Alper H. *J. Am. Chem. Soc.* **1996**, 118, 4264.
9. Larock R. C. *Comprehensive Organic Transformation*, VCH: New York, **1989**.
10. a) Florio S., Troisi L. *Tetrahedron Lett.* **1992**, 33, 7953. b) Florio S., Capriati V., Luisi R. *Tetrahedron Lett.* **1996**, 37, 4781.
11. The typical experimental procedure of the intermolecular cyclocarbonylation:
    A mixture of 1.0 mmol of 4-allylestrone **5**, 0.010 mmol of $Pd(OAc)_2$, and 0.04 mmol of dppb was dissolved in 5 mL of toluene and placed in a 45 mL autoclave. The autoclave was purged, pressurized, (600 psi of CO + H_2) and then heated (110-120 °C). After 24 h the reaction was cooled to room temperature, filtered through Celite and concentrated by rotary evaporation. The separation and the purification of the lactones was achieved by silica gel chromatography and by HPLC. The epoxidation reagent **1** was prepared *in situ* by literature procedure described in the Ref. 10a. Reagents **2** and **3** were prepared as reported: **2** (Ref. 10b); **3** (Abbotto A., Bradamante S., Florio S., Capriati V. *J. Org. Chem.* **1997**, 62, 8937).
    The typical experimental procedure for the epoxidation reaction is described in Ref. 10b. The estrone derivatives were identified by elemental analysis, by IR, NMR and MS techniques, and showed satisfactory spectral data [3,8,10].
12. Miescher K., Scholz C. *Helv. Chim. Acta* **1937**, 20, 1237.
13. Patton T. L. *J. Org. Chem.* **1962**, 27, 910.
    It's worth noting that only for the less polar isomer **8a** a NOE was observed between the H-C(19) and the C-18 angular methyl group (Scheme 1). Therefore, this epoxide should be an α-epoxide (i.e. the oxygen of the epoxide ring was α-oriented according to the commonly accepted α- and β-nomenclature in steroids) with the above mentioned groups at the least distance (1.94 Å by molecular modelling). On the other hand, for the more polar isomer **8b**, NOEs were observed between the H-C(19) and undefined methylene groups, but no NOEs between these groups and benzothiazolyl hydrogens. For both isomers, the chemical shift range of the methylene hydrogens was always the same with no particular shielding effect. We have also looked at chemical shift evidence. A downfield shift was noticed for the H-C(19) (4.5 *vs.* 4.3 δ) on going from one isomer to the other. This trend was analogous (4.2 *vs.* 4.0 δ) to that noticed in similar *E* configured epoxy picolyl derivatives of 5-androstene on going from a β- to an α-epoxide probably owing to the anisotropy of the C-18 angular methyl group shielding methine epoxy hydrogen when this lies on its same side. Based on this evidence, we believe that our epoxides, belong to the *E*-series and have opposite configuration at the C-17 and C-19 atoms as depicted in Scheme 1.
14. Miljkovic D., Gasi K., Kindjer M., Stankovic S., Argay G. *Tetrahedron* **1987**, 43, 631.