Pergamon

Tetrahedron Letters 42 (2001) 7707–7709

TETRAHEDRON LETTERS

Regioselective electrophilic oxidation of a 5-amino-*endo*-tricyclo[5.2.1.0^{2,6}]decenyl enaminone. Synthesis of a novel heterocyclic compound

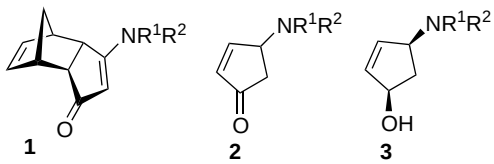
Namakkal G. Ramesh,† Antonius J. H. Klunder and Binne Zwanenburg*

Department of Organic Chemistry, NSR Center for Molecular Structure, Design and Synthesis, University of Nijmegen, Toernooiveld 1, 6525 ED Nijmegen, The Netherlands

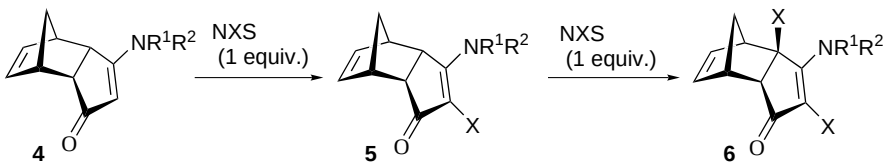
Received 13 July 2001; accepted 30 August 2001

Abstract—An unexpected tandem regioselective oxidation and cyclization of 5-((*S*)-2′-hydroxymethylpyrrolidin-1′-yl)-*endo*-tricyclo[5.2.1.0^{2,6}]deca-4,8-dien-3-ones **7** is reported. The reaction proceeds smoothly to afford novel tetracyclic compounds **8** and **9** in good yield, The structure of **8** was established by single-crystal X-ray analysis. Surprisingly, the C8–C9 norbornene double bond remains intact under these oxidative conditions. © 2001 Elsevier Science Ltd. All rights reserved.

β-Enaminones are interesting structures as they are a composite of an α,β-unsaturated enone and an enamine sub-unit. As a consequence, these compounds have a pronounced ambident character and can react both as nucleophiles and electrophiles. It was recognized that cyclic β-enaminones are valuable precursors for the synthesis of important nitrogen containing pharmacologically active compounds.[1] In recent papers, we have reported an efficient and diastereoselective synthesis of 5-amino-*endo*-tricyclo[5.2.1.0^{2,6}]deca-4,8-dien-3-ones **1**[2] and their use in the synthesis of enantiopure 4-aminocyclopenten-2-ones **2**,[3] which are excellent starting compounds for the enantioselective synthesis of aminocyclopentenols **3**.[4] It was also demonstrated that these tricyclic enaminones possess unexpected chemical behavior wherein the usually highly reactive C8–C9 norbornene double bond remained intact during an electrophilic halogenation, which was rather surprising (Scheme 1).[5] In this paper, we report yet another example of remarkable regioselective behavior by way of an electrophilic oxidation involving the enaminone double bond.



In contrast to their reduction,[4,6] oxidation of enaminones has not been explored much. Except for a few scattered reports on photochemical[7] and electrochemical oxidation,[8] little is known about the chemical oxidation of enaminones. Oxidative cleavage of olefins, particularly that of a norbornene, has been carried out with a number of reagents such as $KMnO_4$,[9] OsO_4,[10] O_3,[11] $RuO_2/NaIO_4$,[12] $RuCl_2/NaIO_4$,[13] and Mn_2O_7.[14] When enaminone[2] **7a** was treated with $NaIO_4$ in the



Scheme 1.

Keywords: regioselective oxidation; tandem oxidation cyclization; enaminone; tetracyclic compound.

* Corresponding author. Tel.: +31-24-3653159; fax: +31-24-3653393; e-mail: zwanenb@sci.kun.nl

† Present address: Department of Chemistry, Indian Institute of Technology-Delhi, Hauz Khas, New Delhi 110 016, India.

PII: S0040-4039(01)01636-7

presence of a cat. amount of RuO_2 in a $CH_3CN/CCl_4/H_2O$ solvent mixture,[15] complete consumption of starting material was observed in about 2 h (tlc). Workup followed by purification using column chromatography afforded a product whose structure has been established as **8** by single-crystal X-ray analysis (Fig. 1),[16] as the spectral data (NMR, IR) were not sufficiently informative. The formation of this product is rather unexpected. Surprisingly, under these conditions, oxidation of the norbornene double bond was not observed at all. This reaction was also successful with the other diastereomer **7b** to afford **9**, the structure of which was assigned by comparison of the spectroscopic data with those of **8** (Scheme 2).

The mechanism of formation of **8** can be envisaged as depicted in Scheme 3. Oxidative cleavage of the enaminone double results in the α-keto aldehyde **10**. Further oxidation to the α-keto acid **11** and subsequent lactonization leads to the product **8**.

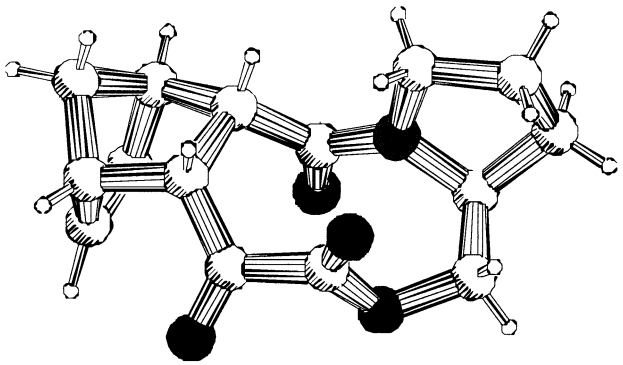
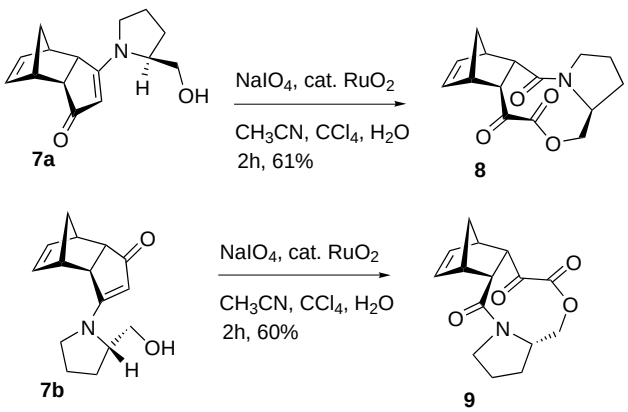


Figure 1. Pluto structure of **8**.

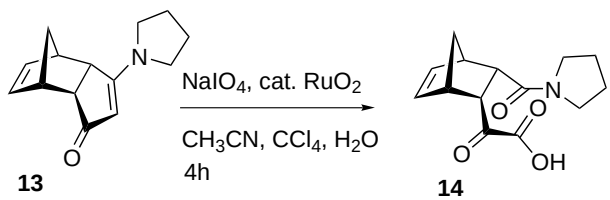


Scheme 2.

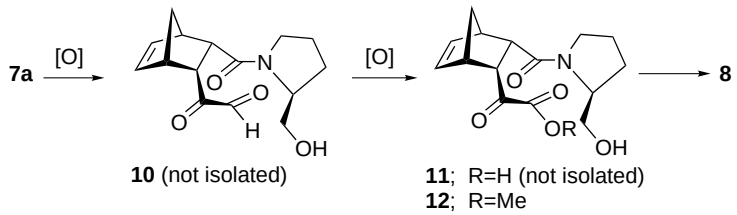
Evidence for the formation of the α-keto acid **11** is also provided by the following additional experiments. Shorter reaction time (45 min) led to incomplete formation of the cyclized product **8** and afforded another product, which after purification by column chromatography (silica gel, ethyl acetate:methanol = 4:1) was identified to be **12**, the methyl ester of **11**. It is quite clear that the product **12** must have been formed from the acid during the chromatographic purification in the presence of silica gel and methanol. The reaction was also carried out with pyrrolidine enaminone **13**, where the final cyclization step is not possible. Enaminone **13** also underwent this oxidation. The formation of the expected α-keto acid **14** was inferred from the mass spectral data (both EI and CI) of the crude reaction mixture as the isolation of **14** was very difficult (Scheme 4).

The complete inertness of the C8–C9 norbornene double bond towards $NaIO_4/RuO_2$ is quite remarkable and seems typical for the tricyclic enaminones. Ozonolysis resulted in a complex mixture of products. Use of *m*-CPBA did not bring about any reaction. This oxidation reaction was also found to be typical for tertiary enaminones only. With the α-methylbenzyl enaminone, a secondary enaminone, no reaction was observed at all even after stirring the reaction mixture for a day.

In conclusion, we have shown that the tricyclic enaminone **7** undergoes an unprecedented electrophilic oxidation of the enaminone double bond and in situ lactonization to afford a novel norbornene annelated 9-membered ring lactone. This reaction is yet another illustration of the inertness of the norbornene double bond in these tricyclic enaminones. The 9-membered heterocyclic ring structure of **8** is quite unusual and justifies further exploration of its chemical and biological properties.[17]



Scheme 4.



Scheme 3.

References

1. (a) Lue, P.; Greenhill, J. V. *Adv. Heterocyclic Chem.* **1996**, *67*, 207; (b) Comins, D. L.; Chen, X.; Joseph, S. P. *Tetrahedron Lett.* **1996**, *37*, 9275; (c) Sato, M.; Aoyago, S.; Yago, S.; Kibayashi, C. *Tetrahedron Lett.* **1996**, *37*, 9063; (d) Bartoli, G.; Marcantoni, E.; Petrini, M.; Sambri, L. *Chem. Eur. J.* **1996**, *2*, 913; (e) Shawe, T. T.; Hanse, D. B.; Peet, K. A.; Prokopowicz, A. S.; Robinson, P. M.; Cannon, A.; Dougherty, K. E.; Ross, A. A.; Landino, L. M. *Tetrahedron* **1997**, *53*, 1547; (f) Ferraz, H. M. C.; de Oliveira, E. O.; Payret-Arrua, M. E.; Brandt, C. A. *J. Org. Chem.* **1995**, *60*, 7357 and references cited therein; (g) Bejan, E.; Haddou, H. A.; Daren, J. C.; Balavoine, G. G. A. *Synthesis* **1996**, 1012.
2. Bakkeren, F. J. A. D.; Ramesh, N. G.; de Groot, D.; Klunder, A. J. H.; Zwanenburg, B. *Tetrahedron Lett.* **1996**, *37*, 8003.
3. Ramesh, N. G.; Klunder, A. J. H.; Zwanenburg, B. *Tetrahedron Lett.* **1998**, *39*, 1429.
4. Ramesh, N. G.; Klunder, A. J. H.; Zwanenburg, B. *J. Org. Chem.* **1999**, *64*, 3635.
5. Ramesh, N. G.; Heijne, E. H.; Klunder, A. J. H.; Zwanenburg, B. *Tetrahedron Lett.* **1998**, *39*, 3295.
6. Comins, D. L.; Brooks, C. A.; Ingalls, C. L. *J. Org. Chem.* **2001**, *66*, 2181 and references cited therein.
7. Orito, K.; Manske, R. H.; Rodrigo, R. *J. Am. Chem. Soc.* **1974**, *96*, 1944.
8. (a) Tabakovic, I. *Electrochim. Acta* **1995**, *40*, 2809; (b) Sanicanin, Z.; Tabakovic, I. *Electrochim. Acta* **1988**, *33*, 1601.
9. (a) Goeksu, S.; Altundas, R.; Suetbeyaz, Y. *Synth. Commun.* **2000**, *30*, 1615; (b) Hoffmann, J.; Voss, J. *Chem. Ber.* **1992**, *125*, 1415; (c) Hronowski, L. J.; Szarek, W. A. *Can. J. Chem.* **1988**, *66*, 61; (d) Della, E. W.; Tsanaktsidis, J. *Aust. J. Chem.* **1985**, *38*, 1705.
10. Henry, J. R.; Weinreb, S. M. *J. Org. Chem.* **1993**, *17*, 4745.
11. (a) Lecollinet, G.; Rachel, A.-V.; Danel, M.; Benvegnu, T.; Mackienzie, G. *J. Org. Chem.* **1999**, *64*, 3139; (b) Chenevert, R.; Martin, R. *Tetrahedron: Asymmetry* **1992**, *3*, 199.
12. Balo, M. C.; Fernandez, F.; Lens, E.; Lopez, C. *Nucleosides Nucleotides* **1996**, *15*, 1335.
13. Ben, R. N.; Breau, L.; Bensimon, C.; Durst, T. *Tetrahedron* **1994**, *50*, 6061.
14. Troemel, M.; Russ, M. *Angew. Chem.* **1987**, *99*, 1037.
15. Mehta, G.; Murthy, A. N. *J. Org. Chem.* **1987**, *52*, 2875.
16. de Gelder, R.; Smits, J. M. M.; Ramesh, N. G.; Klunder, A. J. H. X-Ray data will be published elsewhere. Crystallographic data (excluding structure factors) for the structures in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication number CCDC 167162. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge, CB2 1EZ, UK [fax: +44(0)-1223-336033 or e-mail: deposit@ccdc.cam.ac.uk].
17. cf. Hayashi, K.; Nozaki, H. *J. Antibiot.* **1999**, *52*, 325.