Available online at www.sciencedirect.com
ScienceDirect
Tetrahedron Letters
Tetrahedron Letters 47 (2006) 6587–6589

Dienyne RCM/Diels–Alder approach for the construction of novel steroid-like polycyclic systems

María José Aldegunde, Eva M. Codesido, Luis Castedo and Juan R. Granja*

Departamento de Química Orgánica e Unidade Asociada ó CSIC, Facultade de Química, Universidade de Santiago, 15782 Santiago de Compostela, Spain

Received 12 June 2006; revised 29 June 2006; accepted 6 July 2006
Available online 1 August 2006

Abstract—Our studies directed towards the preparation of novel steroid-like derivatives using RCM reactions are described. The strategy here described was applied to the construction of novel ring-inserted skeleton-expanded steroid analogs by combination of tandem ring-closing metathesis of lineal dienynes and Diels–Alder reaction.

Steroids constitute an extensive and important class of biologically active polycyclic compounds that are widely used for therapeutic purposes.[1] Many functional and structural modifications of steroids have recently been investigated in order to extend their already broad range of biological activities and to increase their selectivity. The numerous methods that have been used to synthesize these and other polycyclic frameworks while achieving precise location of functional groups have generally required a large number of chemical transformations. However, domino or tandem reactions, in which several bonds are formed sequentially without isolation of intermediates, changes in the reaction conditions or addition of reagents, are rapidly gaining ground.[2] Although understanding of such processes is still imperfect, their chemical efficiency, low waste production and low labor demands make them both ecologically and economically attractive. The inclusion of transition-metal-mediated transformations in such sequences, in particular Pd-catalyzed cross-coupling, is well documented.[3] Ring-closing metathesis (RCM) has become a powerful tool for the construction of a variety of cyclic structures that would be difficult to achieve using traditional methods.[4] More recently the highly atom-economical ring-closing enyne metathesis reaction (RCEYM), in which reorganization of a C=C and C≡C bonds produces a 1,3-diene, has begun to have a growing number of applications.[5] Ring-closing dienyne metathesis (RCDEYM) reaction can be considered as a tandem metathesis: an initial RCEYM reaction provides a new metalocarbene that then undergoes RCM with the second double bond to give a second ring (Fig. 1).[6] This transformation is very useful for the construction of two-ring systems from acyclic starting materials, and has even been extended to the construction of three or four rings: for example, the steroid skeleton has in this way been prepared in one step from a linear dienetriyne.[7]

Recently, we described how the use of RCDEYM can be applied to the preparation of steroid-like polycyclic systems incorporating an eight-membered ring such as taxosteroids or transition state analogues of the previtamin D_3–vitamin D_3 isomerization.[8,9] We envisaged

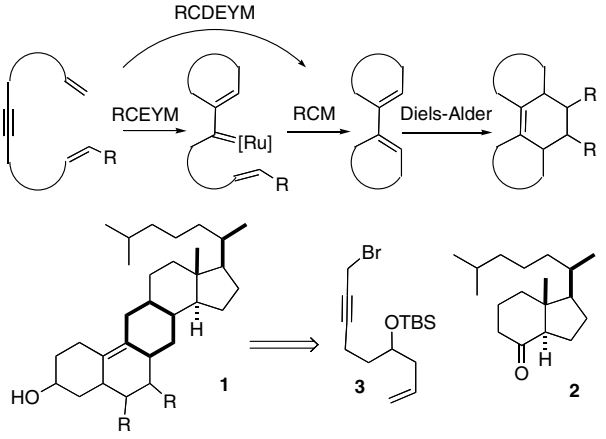


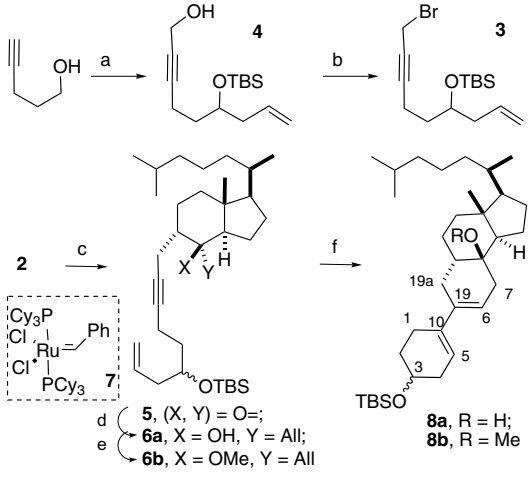
Figure 1.

* Corresponding author. Tel.: +34 981 563100x14251; fax: +34 981 595012; e-mail: qojuangg@usc.es

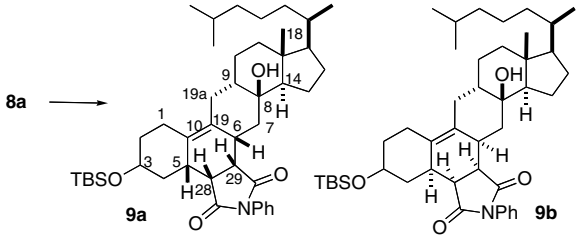
0040-4039/$ - see front matter © 2006 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetlet.2006.07.040

that the use of dienynes with internal alkynes would provide a 1,1′-bicyclic diene system that could be used in a Diels–Alder reaction to generate in two steps four carbon–carbon bonds and a tricyclic system (Fig. 1).[10] Here we describe the implementation of this RCDEYM/Diels–Alder sequence for the preparation of novel ring-inserted skeleton-expanded steroid analogs such as **1**.[11] The required lineal dienyne substrate could be formed by α-alkylation of the kinetic enolate of ketone **2** with bromoenyne **3**, followed by allylation of the carbonyl carbon.

Bromide **3** was prepared in 70% by treatment of alcohol **4** with PPh_3 and CBr_4 (Scheme 1). The alcohol **4** had already been prepared from 4-pentyn-1-ol in the course of previous works on analogues of vitamin D[12] and the pre D_3–D_3 transition state.[9,13] Reaction of 2 equiv of freshly prepared bromide **3** with the kinetic enolate of Grundmann's ketone (**2**),[14] formed by LDA treatment of **2** at −78 °C, afforded ketone **5** in 46% yield. The resulting ketone was subsequently allylated with 4 equiv of allylmagnesium bromide to give dienyne **6a** in 36% yield from **2** as an inseparable 1:1 mixture of diastereomers at C3. To our satisfaction, RCDEYM of **6a** with 15% of Grubbs' ruthenium catalyst (**7**) in refluxing dichloromethane then afforded the diene **8a** in 66%, showing the feasibility of the new tandem process. Even higher yields were obtained with methyl ether **6b**, obtained by refluxing a THF solution of **6a** in the presence of potassium hydride, 18-crown-6 ether and methyl iodide, that afforded tetracyclic product **8b** in 93% yield.



Scheme 1. (a) See Ref. 13; (b) Ph_3P, CBr_4, CH_2Cl_2, 70%; (c) LDA, THF and then **3**, 46%; (d) AllylMgBr, THF, −80 °C, 78%; (e) KH, MeI, crown ether, THF, Δ, 98%; (f) **7**, CH_2Cl_2, Δ, (66% for **8a**, 93% for **8b**).



Scheme 2. *N*-Phenylmaleimide, benzene, Δ, 82%.

To avoid formation of regioisomer mixtures and in order to proof the RCEYM/Diels–Alder approach concept we decided to use a symmetrical dienophile such as *N*-phenylmaleimide. Thus Diels–Alder reaction of **8a** with *N*-phenylmaleimide in refluxing benzene for 8 h provided cycloaddition products **9** in 82% yield (Scheme 2). After flash chromatography purification, only two isomers were isolated in a 2:1 ratio, both diastereomers were assigned as the endo-adducts based on the NMR analysis.

The probably relative stereochemistry of these two isomers (**9a** and **9b**) was assigned based on the inspection of their NMR (NOE, NOESY) spectra and compared with the simulated NOE effects[15] for the most stable conformations of the four cycloaddition products (Fig. 2).[16] The major product was assigned as the endo product **9a** based on the NOE between the H5–H28 and H6–H29, confirming their cis relationship and also by the significant interaction between the H5–H6 and H6–H9, supporting the boat conformations predicted by the semiempirical calculations. The other isomer was assigned as **9b** based on the strong NOE interaction between the H5–H28 and H6–H29 hydrogens, confirming again their cis relationship.

To sum up, in this work we successfully used the tandem ring-closing dienyne metathesis reaction RCDEYM combined with a Diels–Alder reaction to obtain a novel hexacyclic steroid-like compound **9**. We anticipate that it would also be useful for the construction of complex polycyclic systems from conformationally cycloalkanones other than those used in this study. Work on the introduction of additional functional groups and on the biological and pharmacological properties of this new class of compounds, is currently under way.

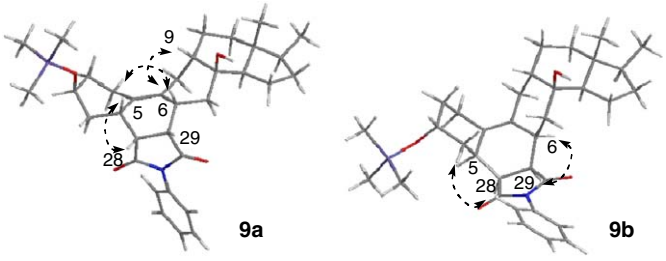


Figure 2.

Acknowledgements

This work was supported by the Ministerio de Ciencia y Tecnología (SAF2004-01044) and the Xunta de Galicia (PGIDIT02PXIC20902PN). M.J.A. thanks the Ministerio de Educación y Ciencia (FPU) for fellowships awarded.

Supplementary data

General methods, synthetic method for preparation of **3**, **5**, **6**, **8**, **9a** and **9b** and ^{1}H and ^{13}C NMR spectra of all compounds. Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2006.07.040.

References and notes

1. (a) Amagata, T.; Amagata, A.; Tenney, K.; Valeriote, F. A.; Lobkovsky, E.; Clardy, J.; Crews, P. *Org. Lett.* **2003**, *5*, 4393–4396; (b) Wu, J. H.; Batist, G.; Zamir, L. O. *Anti-Cancer Drug Des.* **2001**, *16*, 129–133; (c) Biellmann, J.-F. *Chem. Rev.* **2003**, *103*, 2019–2033.
2. For reviews see: (a) Hoffmann, H. M. R. *Angew. Chem., Int. Ed. Engl.* **1992**, *31*, 1332–1334; (b) Ho, L. L. *Tandem Organic Reactions*; Wiley: New York, 1992; (c) Tietze, L. F.; Beifuss, U. *Angew. Chem., Int. Ed. Engl.* **1993**, *32*, 131–163; (d) Bunce, R. A. *Tetrahedron* **1995**, *48*, 13103–13159; (e) Tietze, L. F. *Chem. Rev.* **1996**, *96*, 115–136; (f) McCarroll, A. J.; Walton, J. C. *Angew. Chem., Int. Ed.* **2004**, *40*, 2224–2248.
3. *Metal-Catalyzed Cross-Coupling Reactions*; Diederich, F., Stang, P. J., Eds.; Wiley-VCH: Weinheim, 1997; For multiple Heck-type cross-couplings, see: (a) Tao, W.; Nesbitt, S.; Heck, R. F. *J. Org. Chem.* **1990**, *55*, 63–69; (b) Lansky, A.; Reiser, O.; de Meijere, A. *Synlett* **1990**, 405–407; (c) Trost, B. M.; Dumas, J.; Villa, M. J. *J. Am. Chem. Soc.* **1992**, *114*, 9836–9845; (d) Overman, L. E.; Ricca, D. J.; Tran, V. D. *J. Am. Chem. Soc.* **1993**, *115*, 2042–2044; (e) Thielges, S.; Meddah, E.; Bisseret, P.; Eustache, J. *Tetrahedron Lett.* **2004**, *45*, 907–910; (f) Mal, S. K.; Ray, D.; Ray, J. K. *Tetrahedron Lett.* **2004**, *45*, 277–279.
4. (a) For reviews on metathesis, see: *Handbook of Metathesis*; Grubbs, R. H., Ed.; Wiley-VCH: Weinheim, Germany, 2003; (b) Fürstner, A. *Angew. Chem., Int. Ed.* **2000**, *39*, 3012–3043; (c) Connon, S. J.; Blechert, S. *Angew. Chem., Int. Ed.* **2003**, *42*, 1900–1923; (d) Grubbs, R. H. *Tetrahedron* **2004**, *60*, 7117–7140; For a review on metathesis reactions in total synthesis, see: (e) Nicolaou, K. C.; Bulger, P. G.; Sarlah, D. *Angew. Chem., Int. Ed.* **2005**, *44*, 4490–4527.
5. For reviews on dienyne metathesis, see: (a) Maifeld, S. D.; Lee, D. *Chem. Eur. J.* **2005**, *11*, 6118–6126; (b) Diver, S. T.; Giessert, A. J. *Chem. Rev.* **2004**, *104*, 1317–1382; (c) Diver, S. T.; Giessert, A. J. *Synthesis* **2004**, 466–471; (d) Mori, M. In *Handbook of Metathesis*; Grubbs, R. H., Ed.; Wiley-VCH: Weinheim, Germany, 2003; Vol. 2, pp 176–204; (e) Poulsen, C. S.; Madsen, R. *Synthesis* **2003**, 1–18; (f) Aubert, C.; Buisine, O.; Malacria, M. *Chem. Rev.* **2002**, *102*, 813–834.
6. For some examples of dienyne metathesis, see: (a) Kim, S.-H.; Bowden, N.; Grubbs, R. H. *J. Am. Chem. Soc.* **1994**, *116*, 10801–10802; (b) Renaud, J.; Graf, C.-D.; Oberer, L. *Angew. Chem., Int. Ed.* **2000**, *39*, 3101–3104; (c) Boyer, F.-D.; Hanna, I. *Tetrahedron Lett.* **2002**, *43*, 631–633; (d) Simizu, K.; Takimoto, M.; Mori, M. *Org. Lett.* **2003**, *5*, 2323–2325; (e) Wu, C.-J.; Madhushaw, R. J.; Liu, R.-S. *J. Org. Chem.* **2003**, *68*, 7889–7892; (f) Honda, T.; Namiki, H.; Kaneda, K.; Mizutani, H. *Org. Lett.* **2004**, *6*, 87–89; (g) Boyer, F.-D.; Hanna, I.; Ricard, L. *Org. Lett.* **2004**, *6*, 1817–1820; (h) Peppers, B. P.; Diver, S. T. *J. Am. Chem. Soc.* **2004**, *126*, 9524–9525; (i) Maifeild, S. V.; Miller, R. L.; Lee, D. *J. Am. Chem. Soc.* **2004**, *126*, 12228–12229; (j) González-Gómez, A.; Domínguez, G.; Pérez Castells, J. *Tetrahedron Lett.* **2005**, *46*, 7267–7270; (k) Boyer, F.-D.; Hanna, I. *Eur. J. Org. Chem.* **2006**, 471–478.
7. Zuercher, W. J.; Scholl, M.; Grubbs, R. H. *J. Org. Chem.* **1998**, *63*, 4291–4298.
8. (a) Codesido, E. M.; Castedo, L.; Granja, J. R. *Org. Lett.* **2001**, *3*, 1483–1486; (b) García-Fandiño, R.; Codesido, E. M.; Sobarzo-Sánchez, E.; Castedo, L.; Granja, J. R. *Org. Lett.* **2004**, *6*, 193–196.
9. For RCM/Heck cyclization approach to analogues of [1,7]-H TS, see: (a) Codesido, E. M.; Rodríguez, J. R.; Castedo, L.; Granja, J. R. *Org. Lett.* **2002**, *4*, 1651–1654; (b) García-Fandiño, R.; Aldegunde, M. J.; Codesido, E. M.; Castedo, L.; Granja, J. R. *J. Org. Chem.* **2005**, *70*, 8281–8290.
10. For the sequential metathesis/Diels–Alder approach, see: (a) Yang, Y.-K.; Tae, J. *Synlett* **2003**, *13*, 2017–2020; (b) Saito, N.; Sato, Y.; Mori, M. *Org. Lett.* **2002**, *4*, 803–805; (c) Guo, H.; Madhushaw, R. J.; Shen, F.-M.; Liu, R.-S. *Tetrahedron* **2002**, *58*, 5627–5637; (d) Banti, D.; North, M. *Tetrahedron Lett.* **2002**, *43*, 1561–1564; (e) Efskind, J.; Romming, C.; Undheim, K. *J. Chem. Soc., Perkin Trans. 1* **2001**, 2697–2703; (f) Schurer, S. C.; Blechert, S. *Chem. Commun.* **1999**, 1203–1204; (g) Hoye, T. R.; Donalson, S. M.; Vos, T. *Org. Lett.* **1999**, *1*, 277–279.
11. For a recent preparation of the steroid skeleton by a Heck reaction followed by a Diels–Alder reaction, see: Sünnemann, H. W.; Meijere, A. *Angew. Chem., Int. Ed.* **2004**, *43*, 895–897.
12. (a) Havinga, E. *Experientia* **1973**, *29*, 1181–1192; (b) Okamura, W. H.; Midland, M. M.; Hammond, M. W.; Rahman, N. A.; Dormanen, M. C.; Nemere, I.; Norman, A. W. *J. Steroid Biochem. Mol. Biol.* **1995**, *53*, 603–613; (c) Tian, X. Q.; Holick, M. F. *J. Biol. Chem.* **1999**, *274*, 4174–4179.
13. Codesido, E. M.; Cid, M. M.; Castedo, L.; Mouriño, A.; Granja, J. R. *Tetrahedron Lett.* **2000**, *41*, 5861–5864.
14. Ketone **2** is readily obtained by ozonolysis of vitamin D_3, see: Mascareñas, J. L.; Sarandeses, L.; Castedo, L.; Mouriño, A. *Tetrahedron* **1991**, *47*, 3485–3498.
15. For the NOE simulations we used the program NOEPROM (version 4.0).
16. It was impossible to unequivocally establish the C3 stereochemistry for both RCM or cycloaddition products on the basis of NMR experiments.