Tetrahedron Letters 55 (2014) 679–681

Contents lists available at ScienceDirect

Tetrahedron Letters

journal homepage: www.elsevier.com/locate/tetlet

Synthesis of the bicyclo[6.2.1]undecane ring system by a solvent-free Diels–Alder reaction

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ARTICLE INFO

Article history:
Received 26 October 2013
Revised 26 November 2013
Accepted 29 November 2013
Available online 10 December 2013

Keywords:
Furanoheliangolide
Sesquiterpene
Diels–Alder
Solvent-free
DFT calculations

ABSTRACT

A bicyclo[6.2.1]undecane model compound of the core structure of the biologically active furanoheliangolide sesquiterpene was synthesized. This new and short route was developed by using a solvent-free Diels–Alder reaction between cyclopentadiene and 3-nitro-2-cyclohexenone, followed by simple transformations. Theoretical calculations were performed in order to understand reactivity aspects of the cycloaddition.

Bicyclo[6.2.1]undecane ring systems (**1**) are particularly interesting because they can be good precursors of natural products such as the furanoheliangolide sesquiterpene[1,2] goyazensolide (**2**), isolated from *Eremanthus goyazensis*[3] or Cladiellins which are part of a large family of highly oxygenated marine natural products.[4] These natural products present anti-cancer, anti-inflammatory, insecticidal, and schistosomicidal properties,[3,4] and because of these biological activities these compounds have been the synthetic targets of several research groups (Fig. 1).[4–9]

We have been interested in developing synthetic methodologies for these structures by cycloaddition reactions.[10] In a previous publication,[10a] we reported the preparation of the macrocycle **6**, which has many of the structural features of the basic skeleton of the natural product **2**, using a retro-aldol reaction of the keto-alcohol tricycle **5**. This compound was obtained from the Diels–Alder adduct **3**, followed by a four step transformation (Scheme 1).

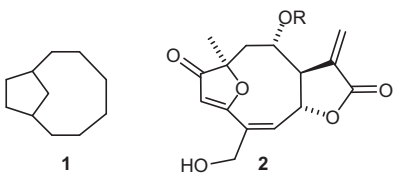
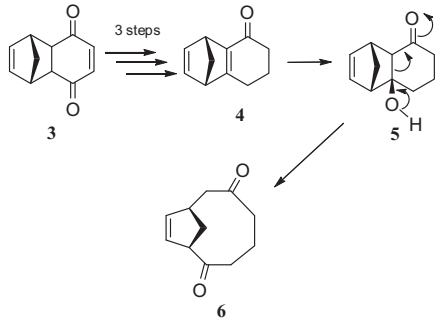


Figure 1.

In this Letter we describe an alternative route to obtain the same intermediate **4**, prepared in the earlier synthesis of **6**. Theoretical calculations were also performed in order to understand some reactivity aspects of the cycloadditions.

The new synthesis consists of a solvent-free Diels–Alder reaction followed by base promoted elimination of HNO_2. Transformation **4** → **5** → **6** was performed in the same manner as previously described.[10a]



Scheme 1.

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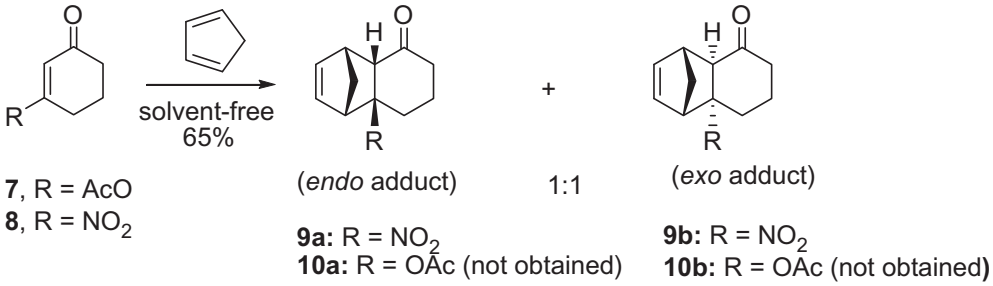
http://dx.doi.org/10.1016/j.tetlet.2013.11.114

In principle, the keto-alcohol **5** could be prepared as the corresponding acetate in one step, by cycloaddition of cyclopentadiene and the enol acetate **7** (Scheme 2). Unfortunately, compound **7** does not react with cyclopentadiene to give the Diels–Alder adducts **10a**–**10b**. We thus decided to use the nitro olefin **8**, which is an excellent substrate for cycloaddition reactions such as Diels–Alder[11] and photocycloadditions,[12] and can be easily prepared from cyclohexanone.[13]

The solvent-free reaction between cyclopentadiene and the nitro compound **8** (cyclopentadiene as solvent, method A) for 48 h, resulted in the two cycloaddition products **9a** and **9b** (Scheme 2) in a 1:1 ratio (verified by ^{1}H NMR) and 65% yield. The diastereoisomers **9a** and **9b** were separated and characterized by IR, ^{1}H, and ^{13}C NMR spectroscopies and mass spectrometry,[14] including the relative stereochemistry determination by NOE experiments (see the Supplementary data). When this reaction was performed in toluene at reflux for 3 h (method B), we obtained the same result with regard to the *endo*/*exo* stereoselectivity. The *exo* adduct **9b** is a crystalline solid, while the *endo* adduct **9a** is a yellowish oil.

In addition to these experimental results, we have performed some DFT calculations for the reactants and transition states (TSs), in order to compare the reactivity of dienophiles **7** and **8**, and also to study the *endo*/*exo* ratio of the adducts **9a** and **9b**. First, we have found a significant difference (ca. 10 kcal mol^{-1}) between the activation energies for the cycloaddition reactions of cyclopentadiene and the nitro-enone **8** with respect to compound **7** (Fig. 2). The reaction between cyclopentadiene and the nitro-enone **8** was much more favorable, explaining the improved reactivity of **8** compared to **7**. Also, we found very similar transition state energies for the *endo* and *exo* products **9a** and **9b**, which is in agreement with the experimental results (1:1 *endo*:*exo* ratio) (Fig. 3).

Thus, we have performed the treatment of each isomer of the Diels–Alder adducts **9a** and **9b**, and also an equimolar mixture, with 1,5-diazabicyclo[4.3.0]non-5-ene (DBN) at room temperature. All the reactions yielded the α,β-unsaturated ketone **4** in 90% after purification (Scheme 3). As described in our previous communication,[10a] enone **4** was hydrated to **5** by treatment with a mixture of acetone/water/*p*-toluenesulfonic acid at reflux. Compound **5** was



Scheme 2.

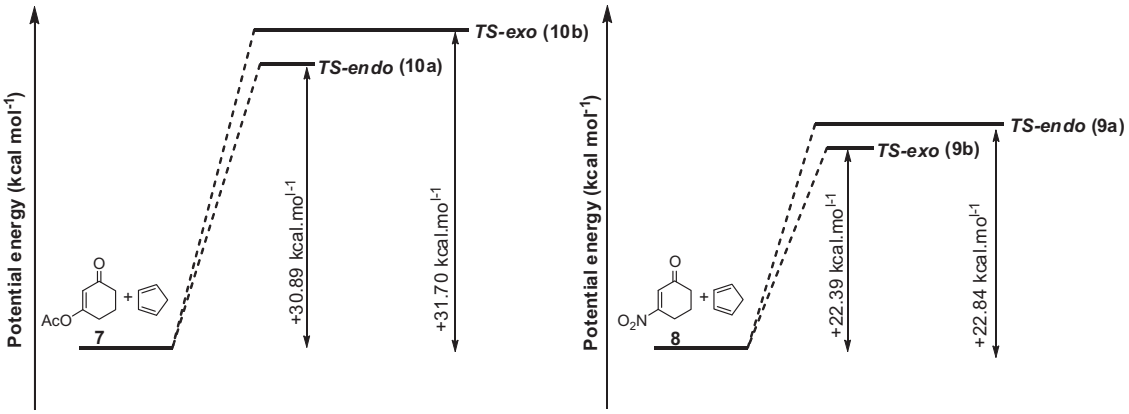


Figure 2. Relative energies of the TSs using the B3LYP/6-31+G(d,p) model for the reaction between cyclopentadiene and compounds **7** or **8**.

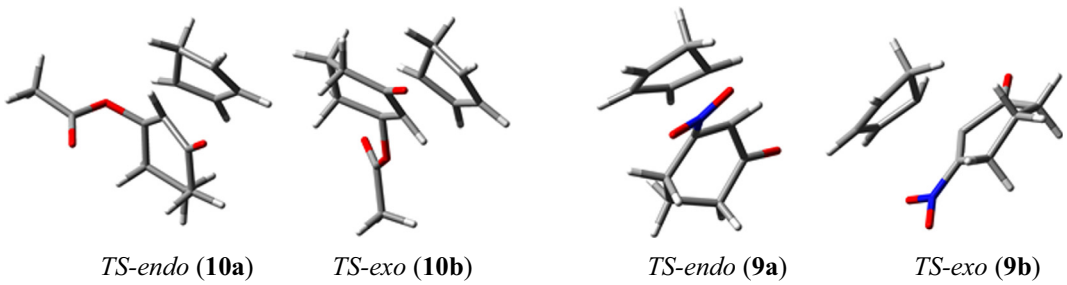
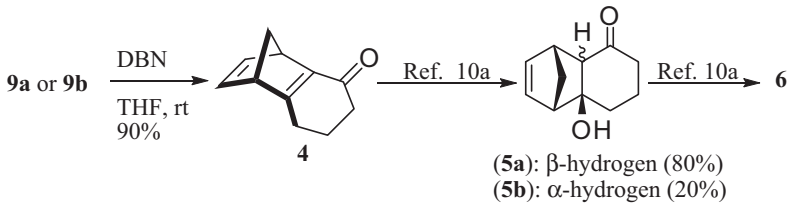


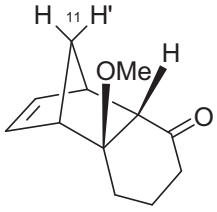
Figure 3. Transition states (TS) **9a**–**9b** and **10a**–**10b**.



Scheme 3.

obtained in 60% yield as an epimeric mixture of **5a** (80%) and **5b** (20%). They were separated by chromatography and characterized by NMR (including NOE experiments). Both isomers were converted to the retro aldol product **6** by treatment with sodium hydride (NaH) in toluene at reflux, in 75% yield after purification.

Compound **4** proved to be very susceptible to Michael addition, when treated with NaOH in methanol/water at room temperature.[15] The stereoselectivity observed in these 1,4-additions was confirmed since the compound **11** was obtained and its structure completely elucidated. This high stereoselectivity is probably due to the cage-like structure of the norbornadiene moiety **4** that permits the addition on only one face of the conjugated double bond.



11

However, after the 1,4-addition of methoxide in **4,** an enolate intermediate is obtained and the protonation on both α and β faces yields two different isomers. Since only one methoxylated compound **11** was formed, we can conclude that the steric accessibility in the two faces of the enolate unit are different (Scheme 3) and we strongly believe that this is a typical case of thermodynamic control where the epimer **11** is thermodynamically accumulated under the equilibrium conditions (methanol/base). It can be reinforced by the experimental and molecular modeling studies involving cyclopentenone annulated norbornadiene systems[16,17] that show the addition of methanol yielding exclusively the *cis*-isomer.

In summary, we describe an alternative, shorter, and efficient method for the synthesis of strained dienone **4**, a precursor of the bicyclo[6.2.1]undecane ring system **6**, using as a key step a solvent-free Diels–Alder reaction. Also, we report a highly stereoselective Michael addition which allows the synthesis of the previously reported compound **6**.

Acknowledgments

The authors thank the Fundação de Amparo à Pesquisa do Estado de São Paulo (FAPESP), the Conselho Nacional de Desenvolvimento Científico e Tecnológico (CNPq), and the Coordenação de Aperfeiçoamento de Pessoal de Nível Superior (CAPES) for financial support. Thanks are also due to Professor Timothy J. Brocksom for the suggestions and grammar corrections.

Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2013.11.114.

References and notes

1. (a) Paquette, L. A.; Pegg, N. A.; Toops, D.; Maynard, G. D.; Rogers, R. D. *J. Am. Chem. Soc.* **1990**, *112*, 277; (b) Paquette, L. A.; Bailey, S. *J. Org. Chem.* **1995**, *60*, 7849; (c) Paquette, L. A.; Montgomery, F. J.; Wang, T. Z. *J. Org. Chem.* **1995**, *60*, 7857; (d) Zeng, Q.; Bayley, S.; Wang, T. Z.; Paquette, L. A. *J. Org. Chem.* **1998**, *63*, 137; (e) Paquette, L. A.; Zeng, Q. *Tetrahedron Lett.* **1999**, *40*, 3823.
2. Minaard, A. J.; Wijnberg, J. B. P. A.; de Groot, A. *Tetrahedron* **1999**, *55*, 2115.
3. Vichnewski, W.; Takahashi, A. M.; Nasi, A. M. T.; Gonçalves, D. C. R. G.; Dias, D. A.; Lopes, J. N. C.; Goedken, V. L.; Gutiérrez, A. B.; Herz, W. *Phytochemistry* **1989**, *28*, 1441.
4. Clark, J. S.; Wong, Y. *Chem. Commun.* **2000**, 1079.
5. Takao, K.; Ochiai, H.; Yoshida, K.; Hashizuka, T.; Koshimura, H.; Tadano, K.; Ogawa, S. *J. Org. Chem.* **1995**, *60*, 8179.
6. Boeckman, R. K., Jr.; Yoon, S. K.; Heckendorn, D. K. *J. Am. Chem. Soc.* **1991**, *113*, 9682.
7. Wang, W.; Roskamp, E. J. *Tetrahedron Lett.* **1992**, *33*, 7787.
8. Jeong, H.; Kim, H.; Kang, H. *Bull. Korean Chem. Soc.* **1997**, *18*, 7.
9. McDougal, P. G.; Oh, Y.; VanDerveer, D. *J. Org. Chem.* **1989**, *54*, 91.
10. (a) Constantino, M. G.; Beatriz, A.; da Silva, G. V. J. *Tetrahedron Lett.* **2000**, *41*, 7001; (b) Constantino, M. G.; de Oliveira, K. T.; Beatriz, A.; da Silva, G. V. J. *Tetrahedron Lett.* **2003**, *44*, 2641; (c) Constantino, M. G.; de Oliveira, K. T.; Beatriz, A.; da Silva, G. V. J. *Magn. Reson. Chem.* **2003**, *41*, 726; (d) Constantino, M. G.; Aragão, V.; da Silva, G. V. J. *Tetrahedron Lett.* **2008**, *49*, 1393.
11. Corey, E. J.; Estreicher, H. *Tetrahedron Lett.* **1981**, *22*, 603.
12. Quevillon, T. M.; Weedon, A. C. *Tetrahedron Lett.* **1996**, *37*, 3939.
13. Vankar, Y. D.; Bawa, A. *Synth. Commun.* **1985**, *15*, 1253.
14. *Compound* ***9a****: rel-*(1*S*, 2*S*,7*S*,8*R*)-7-Nitrotricyclo[6.2.1.0^{2,7}]undec-9-en-3-one: ^{1}H NMR (300 MHz, $CDCl_3$) δ: 1.34 (dt, 1H, J_1 = 15.0 Hz, J_2 = 11.6 Hz, J_3 = 5.2 Hz), 1.35 (d, 1H, J = 9.6 Hz), 1.57 (dt, 1H, J_1 = 9.6 Hz, J_2 = J_3 = 2.3 Hz), 1.76 (m, 1H), 1.77 (m, 1H), 2.00 (dt, 1H, J_1 = 18.0 Hz, J_2 = J_3 = 9 Hz), 2.41 (dddd, 1H, J_1 = 18.0 Hz, J_2 = 5.5 Hz, J_3 = 3.2 Hz, J_4 = 1.5 Hz), 2.55 (m, 1H), 3,35 (m, 1H), 3,58 (m, 1H), 3,87 (d, 1H, J = 4.0 Hz), 6.06 (dd, 1H, J_1 = 5.6 Hz, J_2 = 3.5 Hz), 6.33 (dd, 1H, J_1 = 5.6 Hz, J_2 = 2.8 Hz). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 18.7 (CH_2), 33.9 (CH_2), 37.7 (CH_2), 44.8 (CH), 45.9 (CH_2), 52.8 (CH), 55.7 (CH), 101.2 (C), 132.9 (CH), 141.4 (CH), 209.8 (C=O). IR (film) ν_{max}: 2963, 2872, 1701, 1535, 1459, 1442, 1349, 1323, 738. MS *m*/*z* (rel. intensity): 143 [M$^+$] (9.9%), 131 (49.7%), 117 (27.4%), 105 (38.5%), 91 (100%), 77 (45.8%), 66 (48.8%), 55 (58.1%), 39 (41.3%). *Compound* ***9b****: rel-*(1*S*, 2*S*,7*R*,8*R*)-7-Nitrotricyclo[6.2.1.0^{2,7}]undec-9-en-3-one: mp 87–88 °C, ^{1}H NMR (300 MHz, $CDCl_3$) δ: 1.40 (d, 1H, J = 9.7 Hz), 1.64 (ddt, 1H, J_1 = 9.7 Hz, J_2 = 3.0 Hz, J_3 = J_4 = 1.5 Hz), 1.75 (ddd, 1H, J_1 = 14.0 Hz, J_2 = 12.4 Hz, J_3 = 4.8 Hz), 1.81–2.00 (m, 2H), 2.34 (ddd, 1H, J_1 = 18.5 Hz, J_2 = 10.0 Hz, J_3 = 8.2 Hz), 2.64 (ddt, 1H, J_1 = 18.5 Hz, J_2 = 7.0 Hz, J_3 = J_4 = 2 Hz), 2.72 (m, 1H), 3.15 (d, 1H, J = 3.0 Hz), 3.35 (m, 1H), 3.50 (m, 1H), 6.02 (dd, 1H, J_1 = 5.8 Hz, J_2 = 2.8 Hz), 6.39 (dd, 1H, J_1 = 5.8 Hz, J_2 = 3.1 Hz). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 18.3 (CH_2), 35.6 (CH_2), 37.6 (CH_2), 44.6 (CH), 47.2 (CH_2), 52.2 (CH), 54.3 (CH), 100.4 (C), 134.3 (CH), 138.6 (CH), 209.5 (C=O). IR (KBr) ν_{max}: 2948, 2872, 1705, 1535, 1463, 1357, 1221, 725. MS *m*/*z* (rel. intensity): 159 [M$^+$] (8.6%), 131 (53.6%), 117 (23.1%), 105 (42.5%), 91 (100%), 77 (43.5%), 66 (77.8%), 55 (81.4%), 39 (61.3%).
15. *Compound* ***11****: rel-*(1*S*, 2*S*, 7*S*, 8*R*)-7-Methoxytricyclo[6.2.1.0^{2,7}]undec-9-en-3-one: ^{1}H NMR (300 MHz, $CDCl_3$) δ: 0.95 (m, 1H), 1.51 (dt, 1H, J_1 = 8 Hz, J_2 = J_3 = 1.7 Hz), 1.66 (m, 1H), 1.84 (d, 1H, J = 8 Hz), 1.95–2.10 (m, 2H), 2.23 (m, 1H), 2.38 (m, 1H), 2.54 (d, 1H, J = 4 Hz), 3.06 (m, 1H), 3.20 (br s, 1H), 3.27 (s, 3H), 5.92 (dd, 1H, J_1 = 5.6 Hz, J_2 = 3.5 Hz), 6.25 (dd, 1H, J_1 = 5.6 Hz, J_2 = 2.7 Hz). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 18.1 (CH_2), 28.0 (CH_2), 38.9 (CH_2), 43.5 (CH), 45.4 (CH_2), 47.3 (CH), 49.3 (CH), 62.5 (CH_3), 87.1 (C), 134.1 (CH), 139.9 (CH), 213.9 (C=O).
16. Zhu, J.; Klunder, A. J. H.; Zwanenburg, B. *Tetrahedron* **1994**, *50*, 10597.
17. Zhu, J.; Klunder, A. J. H.; Zwanenburg, B. *Tetrahedron Lett.* **1994**, *35*, 2787.