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Tetrahedron Letters 49 (2008) 1393–1395

Tetrahedron Letters

An approach to the synthesis of furanoheliangolides through Diels–Alder reactions

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Received 21 November 2007; revised 12 December 2007; accepted 14 December 2007

Abstract

The core structure of the natural sesquiterpene lactones furanoheliangolides, an 11-oxabicyclo[6.2.1]undecane system, was synthesized through a pathway involving two Diels–Alder reactions.

Keywords: Synthesis; Natural products; Furanoheliangolides; Diels–Alder reactions

The furan ring system occurs widely in natural products, either as a simple structure unit, or as part of a more complex annulated system.[1–4] Furanoheliangolides are an important class of natural sesquiterpene lactones containing a furanone ring as part of a bicyclic ring system, an 11-oxabicyclo[6.2.1]undecane. Examples of furanoheliangolides isolated from several different plants[5–8] are given in Figure 1.

The biological activity of most furanoheliangolides has attracted the attention of several research groups to investigate the syntheses for these compounds.[9–14] However, the development of efficient methodology for synthesizing the complex bicyclic system is still a challenging task.

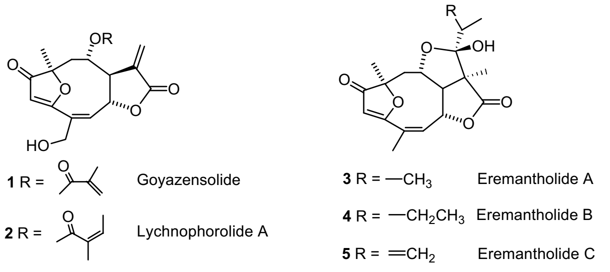
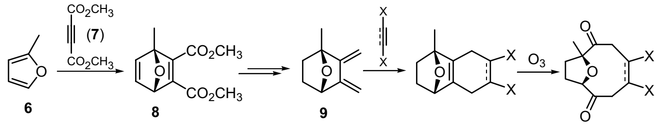


Fig. 1. Examples of furanoheliangolides.

In this Letter we describe an approach involving two Diels–Alder reactions as key steps to build the bicyclic ring system, as depicted in Scheme 1.

Furan rings are usually weak dienes for Diels–Alder reactions, but they are very reactive and give good yields with acetylenic dienophiles.[2] The reaction of 2-methylfuran (**6**) with dimethyl acetylenedicarboxylate (**7**) was already described in the literature using ethyl ether as solvent[15] or without any solvent, in a sealed tube,[16] with yields below 80%. We were able to improve the yield by using toluene as solvent, heating at reflux for 3 h, then adding one more equivalent of **6** and refluxing for one additional hour.[17] The yield, calculated for dienophile **7**, was quantitative (Scheme 2).



Scheme 1. Synthetic approach to the 11-oxabicyclo[6.2.1]undecane ring system.

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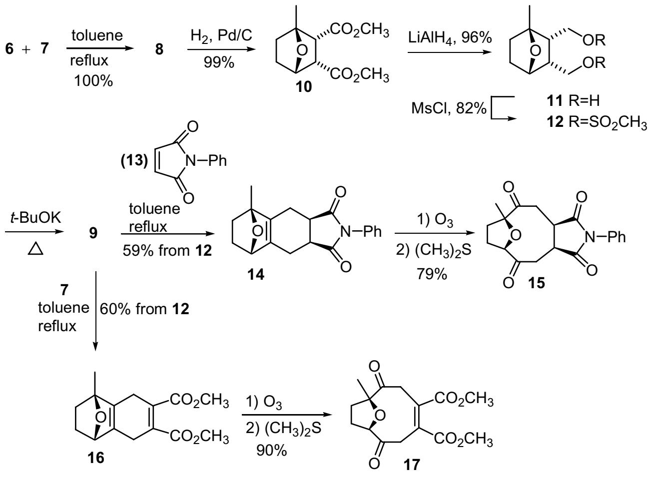
0040-4039/$ - see front matter
doi:10.1016/j.tetlet.2007.12.079



Scheme 2. Synthesis of macrocycles **15** and **17**.

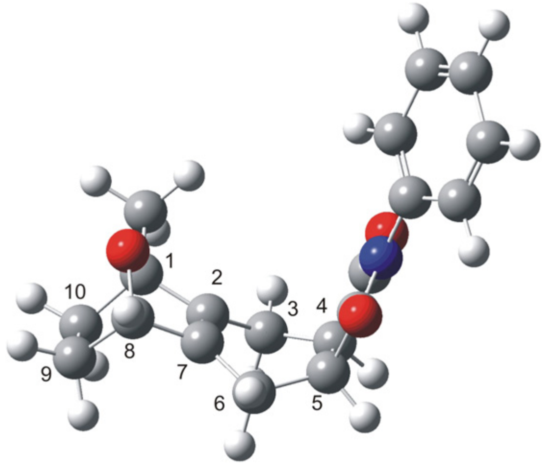


Fig. 2. Most stable conformer of adduct **14**.[25]

Adduct **8**, however, is rather unstable and must be used for the next step immediately after its preparation. Reduction of **8** with H_2 and Pd/C gave the stable diester **10**. As noted before,[18] the W coupling observed for the α-carboxylic hydrogens of **10** confirms the stereochemistry as being *endo*.

Reduction of the ester groups with $LiAlH_4$ (96% yield) and transformation of the resulting diol into the corresponding dimesylate (82% yield) was accomplished without any significant problem. The elimination reaction to produce **9**,[19] however, proved to be a difficult reaction. We obtained good results only by heating the dimesylate with solid *t*-BuOK, without any solvent, in a horizontal distillation oven. The distillate, product **9** containing *t*-BuOH, was used in the next step without any further purification.

The crude diene **9** gave Diels–Alder adducts either with *N*-phenylmaleimide **13** to give **14**[20] or with the acetylenic diester **7** to give **16**.[21] Both reactions were performed in refluxing toluene and gave similar yields. Both products were obtained as white crystals.

Ozonolysis of the double bond of **14** was accomplished by the treatment of an ethyl acetate solution of the substrate at −78 °C with ozone, followed by the addition of methyl sulfide. The desired product **15** was obtained in 79% yield as stable white crystals.[22]

The more nucleophilic double bond of **16** could be ozonized in a strictly similar manner to give the corresponding product **17** in 90% yield.[23] This product is also crystalline, but it is unstable, and must be kept always in solution.

The structure of adduct **16** could be determined through straightforward analysis of NMR spectra, but adduct **14** has an additional stereochemical feature, that required a more detailed study. The main question is the cis/trans orientation of the imide ring relative to the oxygen bridge. Preliminary studies with a molecular mechanics program[24] have indicated that only the cis (or *exo*) orientation shown in Figure 2 could give NOE effect between hydrogens 4/5 and α hydrogens 9/10. As the NOE effect was observed in a NOEDIF experiment, we had a first indication of this stereochemistry.

Table 1
Experimental and Boltzmann averaged *J* values

	Theoretical *J* value (Hz)	Experimental *J* value (Hz)
H-3α/H-4	5.9	7.5
H-3β/H-4	2.0	2.0
H-6α/H-5	6.1	7.7
H-6β/H-5	1.9	2.0

Through detailed examination of ^1H and ^{13}C NMR, DEPT-135, COSY, HMQC, and HMBC spectra we could identify the signals of most hydrogens, but in ^1H NMR, the signals corresponding to H-4 and H-5 are overlapped, as well as the signals of H-10α and H-9α. Through ^1H NMR experiments with shift reagent Eu(fod)$_3$ we observed a larger shift for hydrogens 3β and 6β (as compared to 3α and 6α) and for hydrogen 10β (as compared to 10α), thus confirming the stereochemistry for all hydrogens (hydrogen 9β can be identified through its coupling with H-8, as observed in COSY).

A further confirmation of the stereochemistry of **14** can be obtained from the coupling constant values observed for H-3/H-4 and for H-6/H-5. A conformational search performed with GMMX[25] furnished six different conformations for **14**; the corresponding *J* values were determined and Boltzmann—averaged to give the theoretical values of Table 1. The fair agreement between the theoretical and experimental values confirms the proposed stereochemistry.

In this approach to the synthesis of furanoheliangolides, macrocycles **15** and **17** were prepared in seven steps, involving two Diels–Alder reactions, with overall yields of 36.3% and 42.1%, respectively.

Acknowledgments

The authors thank Professor Norberto Peporine Lopes for the high resolution mass spectra; and the Fundação de Amparo à Pesquisa do Estado de São Paulo (FAPESP), the Conselho Nacional de Desenvolvimento Científico e Tecnológico (CNPq), the Coordenação de Aperfeiçoamento de Pessoal de Nível Superior (CAPES), and the Financiadora de Estudos e Projetos (FINEP) for financial support.

Supplementary data

Detailed experimental procedures, ^{1}H NMR and ^{13}C NMR spectra for the reported compounds. Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2007.12.079.

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20. Compound **14**: $(1R^*,4R^*,5S^*,8S^*)$-*N*-phenyl-1-methyl-11-oxatricyclo-$[6.2.1.0^{2,7}]$undec-2(7)-ene-4,5-dicarboximide: ^{1}H NMR ($CDCl_3$, 500 MHz), δ (ppm): 1.22 (m, 2H); 1.54 (m, 1H); 1.56 (s, 3H); 1.97 (m, 1H); 2.27 (dd, 1H, $J_1 = 17.4$, $J_2 = 7.5$ Hz); 2.39 (dd, 1H, $J_1 = 17.4$, $J_2 = 7.7$ Hz); 2.81 (dd, 1H, $J_1 = 17.4$, $J_2 = 2.0$ Hz); 2.87 (dd, 1H, $J_1 = 17.4$, $J_2 = 2.0$ Hz); 3.27 (m, 2H); 4.74 (d, 1H, $J = 4.5$ Hz); 7.27 (m, 2H); 7.38 (m, 1H); 7.46 (m, 2H). ^{13}C NMR ($CDCl_3$, 125 MHz), δ (ppm): 16.8 (CH_3); 19.2 (CH_2); 20.7 (CH_2); 28.1 (CH_2); 31.3 (CH_2); 37.5 (CH); 37.8 (CH); 79.7 (CH), 86.7 (C); 126.4 (CH); 128.5 (CH); 129.1 (CH); 131.9 (C); 138.7 (C); 139.4 (C); 178.6 (C=O); 178.7 (C=O). IR ν_{max} (KBr): 2938; 1708; 1496; 1380; 1154; 770 cm^{-1}. HRMS (ESI-TOF): calculated for $C_{19}H_{19}NO_3Na$ (MNa^+) 332.1257, found 332.1275. Mp 124–127 °C.
21. Compound **16**: dimethyl$(1R^*,8S^*)$-1-methyl-11-oxatricyclo-$[6.2.1.0^{2,7}]$-undeca-2(7),4-diene-4,5-dicarboxylate: ^{1}H NMR (C_6D_6, 500 MHz), δ (ppm): 1.03 (m, 2H); 1.45 (m, 1H); 1.48 (s, 3H); 1.85 (m, 1H); 2.74 (m, 2H); 3.12 (m, 2H); 3.61 (s, 3H); 3.62 (s, 3H); 4.58 (d, 1H, $J = 4.4$ Hz). ^{13}C NMR (C_6D_6, 125 MHz), δ (ppm): 16.9 (CH_3); 24.4 (CH_2); 25.8 (CH_2); 28.3 (CH_2); 31.7 (CH_2); 51.7 (CH_3); 79.0 (CH); 86.0 (C), 133.4 (C); 133.7 (C); 136.8 (C); 137.3 (C); 168.2 (C=O). IR ν_{max} (KBr): 2954; 1724; 1636; 1436; 2324; 1272; 1056 cm^{-1}. HRMS (ESI-TOF): calculated for $C_{15}H_{19}O_5$ (MH^+) 279.1227, found 279.1240. Mp 72–74 °C.
22. Compound **15**: $(1R^*,4R^*,8S^*,11R^*)$-1-methyl-6-phenyl-14-oxa-6-aza-tricyclo$[9.2.1.0^{4,8}]$tetradecane-2,5,7,10-tetrone: ^{1}H NMR ($CDCl_3$, 400 MHz), δ (ppm): 1.47 (s, 3H); 1.57 (ddd, 1H, $J_1 = 12.4$, $J_2 = 11.6$, $J_3 = 6.6$ Hz); 2.05 (dddd, 1H, $J_1 = 13.1$, $J_2 = 11.6$, $J_3 = 8.8$, $J_4 = 4.3$ Hz); 2.49 (dddd, 1H, $J_1 = 13.1$, $J_2 = 9.8$, $J_3 = 6.6$, $J_4 = 2.5$ Hz); 2.66 (dd, 1H, $J_1 = 14.1$, $J_2 = 2.0$ Hz); 2.70 (d, 1H, $J = 14.1$ Hz); 2.72 (ddd, 1H, $J_1 = 12.4$, $J_2 = 9.8$, $J_3 = 4.3$ Hz); 3.77–3.58 (m, 4H); 4.51 (dd, 1H, $J_1 = 8.8$, $J_2 = 2.5$ Hz); 7.29 (m, 2H); 7.41 (m, 1H); 7.49 (m, 2H). ^{13}C NMR ($CDCl_3$, 100 MHz), δ (ppm): 21.6 (CH_3); 24.9 (CH_2); 31.3 (CH_2); 33.3 (CH_2); 34.3 (CH_2); 39.9 (CH); 40.1 (CH); 84.4 (CH), 89.3 (C); 126.3 (CH); 128.8 (CH); 129.2 (CH); 131.7 (C); 177.3 (C=O); 177.6 (C=O); 209.3 (C=O); 209.4 (C=O). IR ν_{max} (KBr): 2922; 1714; 1498; 1388; 1170; 1056 cm^{-1}. HRMS (ESI-TOF): calculated for $C_{19}H_{20}NO_5$ (MH^+) 342.1336, found 342.1342. Mp 192–196 °C.
23. Compound **17**: dimethyl$(1R^*,4Z,8S^*)$-1-methyl-2,7-dioxo-11-oxabicyclo[6.2.1]undec-4-ene-4,5-dicarboxylate: ^{1}H NMR (CCl_4, 500 MHz, C_6D_6 external lock), δ (ppm): 1.28 (s, 3H); 1.71 (ddd, 1H, $J_1 = 12.8$, $J_2 = 8.2$, $J_3 = 7.9$ Hz); 1.90 (dtd, 1H, $J_1 = 13.0$, $J_2 = J_3 = 7.9$, $J_4 = 7.1$ Hz); 2.14 (ddd, 1H, $J_1 = 12.8$, $J_2 = 7.9$, $J_3 = 5.9$ Hz); 2.25 (dddd, 1H, $J_1 = 13.0$, $J_2 = 8.6$, $J_3 = 8.2$, $J_4 = 5.9$ Hz); 3.03 (d, 1H, $J = 11.0$ Hz); 3.07 (d, 1H, $J = 10.6$ Hz); 3.68 (s, 3H); 3.69 (s, 3H); 4.15 (d, 1H, $J = 11.0$ Hz); 4.29 (d, 1H, $J = 10.6$ Hz); 4.38 (dd, $J_1 = 8.6$, $J_2 = 7.2$ Hz). ^{13}C NMR (CCl_4, 125 MHz, C_6D_6 external lock), δ (ppm): 23.3 (CH_3); 28.6 (CH_2); 34.3 (CH_2); 40.0 (CH_2); 40.5 (CH_2); 51.1 (CH_3); 51.1 (CH_3); 83.7 (CH), 89.9 (C); 130.4 (C); 131.3 (C); 165.1 (C=O); 202.9 (C=O); 204.9 (C=O). IR ν_{max} (KBr): 2918; 1726; 1438; 1270; 1106 cm^{-1}. HRMS (ESI-TOF): calculated for $C_{15}H_{19}O_7$ (MH^+) 311.1125, found 311.1125. Mp 135–139 °C.
24. PCMODEL, version 7.0, Serena Software, PO Box 3076, Bloomington, IN 474-23076.
25. GMMX, version 1.5, Serena Software, PO Box 3076, Bloomington, IN 474-23076.