Available online at www.sciencedirect.com
ScienceDirect
Tetrahedron Letters
Tetrahedron Letters 48 (2007) 4331–4333

An enyne metathesis/Diels–Alder reaction sequence towards the synthesis of cup-shaped 5/5/6-tricyclic architectures

Laurent Evanno, Alexandre Deville, Bernard Bodo and Bastien Nay*

Laboratoire de Chimie et Biochimie des Substances Naturelles, Muséum National d'Histoire Naturelle—CNRS, 57 rue Cuvier (CP54), 75005 Paris, France

Received 20 March 2007; revised 18 April 2007; accepted 24 April 2007
Available online 27 April 2007

Abstract—A strategy to synthesize the 5/5/6-tricyclic framework of presilphiperfolane natural products is described, involving a model dienyne compound (**I**). The key steps are an enyne metathesis reaction to introduce the diene part and a Diels–Alder cycloaddition to reveal the tricyclic architecture.

The 5/5/6-, 5/6/6- and 5/6/7-fused tricyclic frameworks are part of many natural products with cup-shaped architectures, especially in the terpenoid series (Fig. 1).[1] The total synthesis of such intriguing molecular structures has been investigated by others with the extensive use of rearrangement and cycloaddition strategies.[2] We report herein the synthesis and use of a model compound (**I**) toward the presilphiperfolane tricyclic skeleton. Our synthetic strategy involves two key steps: (i) an intramolecular Diels–Alder cycloaddition between an alkyne and a diene resulting from (ii) an enyne metathesis reaction.

As shown in Figure 1 the dienyne structure **I** could be a pivotal intermediate not only for the synthesis of presilphiperfolane analogues (**II**), but also for the construction of homologous structures such as **III**, depending on the type of cycloaddition used. Such a diene was thus synthesized for reactivity survey toward catalytic or thermal conditions. The diene part was installed by $PtCl_2$-catalyzed enyne reorganization while the Corey–Fuchs methodology was used for the terminal alkyne. We show in this Letter that the thermal conditions applied to an activated diene were effective to build the 5/5/6-tricyclic structure.

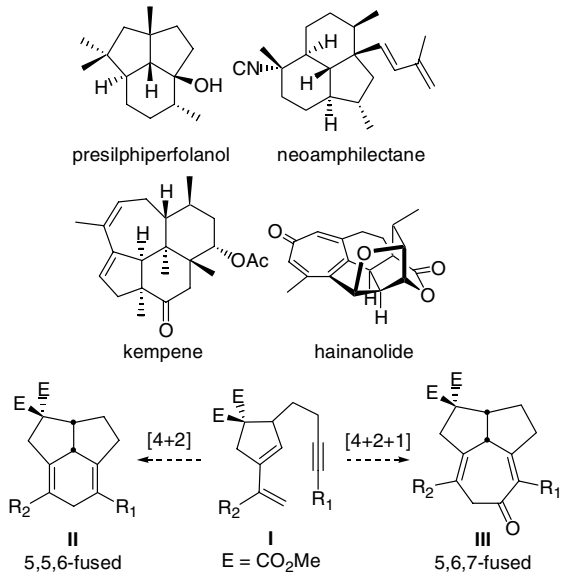
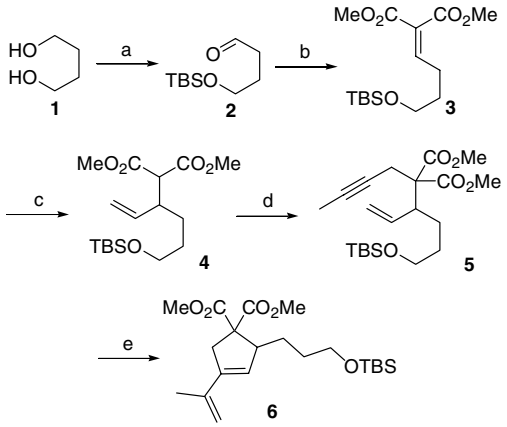


Figure 1. Synthetic strategies toward analogues of cup-shaped natural products from model dienyne **I**.

The cyclopentene part of model compound **I** was rapidly elaborated from butane-1,4-diol (**1**) in a six-step sequence (Scheme 1). The fragile aldehyde **2** was obtained according to the literature[3] by selective protection and subsequent oxidation of the remaining alcohol. Knoevenagel condensation of compound **2** with dimethyl malonate was achieved in the presence of catalytic amounts of L-proline in DMSO,[4] giving α,β-unsaturated diester **3** in 72% yield. The 1,4-addition

Keywords: Enyne metathesis; Diels–Alder cycloaddition; Fused tricyclic structure; Catalysis; Carbonylation.
* Corresponding author. Tel.: +33 1 40 79 56 09; fax: +33 1 40 79 31 35; e-mail: bnay@mnhn.fr

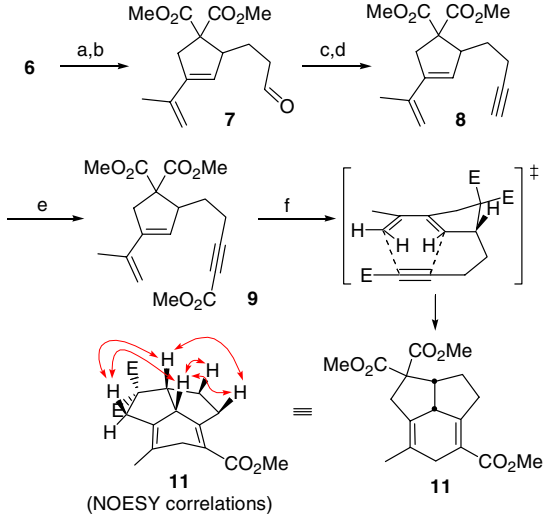
0040-4039/$ - see front matter © 2007 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetlet.2007.04.107



Scheme 1. Reagents and conditions: (a) Two steps according to Ref. 3; (b) $CH_2(CO_2Me)_2$, L-proline (0.1 equiv), DMSO, rt (72%); (c) $CH_2{=}CHMgBr$, CuCN (0.15 equiv), LiCl (0.35 equiv), THF, −78 °C (93%); (d) NaH, then $CH_3C{\equiv}CCH_2Br$, DMF, 0 °C (93%); (e) $PtCl_2$ (0.04 equiv), toluene, 80 °C (79%).

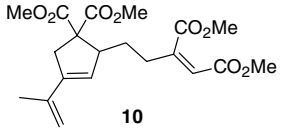
of vinylmagnesium bromide in the presence of catalytic CuCN/LiCl afforded the branched product **4** which was then alkylated after deprotonation in the presence of 2-butynyl bromide to give enyne **5** in excellent yields for the two steps.[5] Enyne reorganization finally delivered diene **6** in 79% yields.[6] Platinum chloride was an efficient catalyst for this reaction which was performed in toluene at 80 °C.[7] Alternatively, any of the Grubbs catalysts were responsible for many side reactions[8] and degradation of the expected product **6**.

Silyl ether **6** was then cleaved and the resulting terminal alcohol oxidized into aldehyde **7** (Scheme 2). Corey–Fuchs alkynylation[9] gave dienyne **8** which was readily transformed into methyl ester **9** by oxidative carbonylation in methanol in the presence of catalytic amounts of palladium chloride and anhydrous copper chloride (61% yield).[10,11]



Scheme 2. Reagents and conditions: (a) TBAF, THF, 0 °C; (b) PCC, NaOAc, DCM, rt (76%, 2 steps); (c) CBr_4, PPh_3, DCM; (d) *n*-BuLi, THF, −78 °C (63%, 2 steps); (e) CO, $PdCl_2$, $CuCl_2$, NaOAc, MeOH, rt (61%); (f) MeCN, 80 °C (83%).

The synthesis of ester **9** was time-dependent and evolved after 15–30 min toward the formation of the double oxidative carboxylation product **10**, isolated in 35% yield after 45 min (careful TLC monitoring of the reaction circumvented this problem).



The last step involved the intramolecular Diels–Alder reaction of dienyne **9**. The reaction could be done by heating **9** in acetonitrile at 80 °C and afforded tricyclic compound **11**.[12] It is noticeable however that the reaction also occurred when leaving the compound at −30 °C for several months (70% yield after 7 months). Attempts to functionalize **9** by 1,4-addition of an iodide on the triple bond for other synthetic purpose in the presence of sodium iodide also furnished cycloadduct **11**, instead of the iodination product in acetonitrile. Alternatively, submitting compound **10** to the same thermolytic conditions gave no reaction probably because of unfavorable steric effects.

Both five-membered rings of compound **11** share a *cis*-junction which is consistent with the transition state shown in Scheme 2. The relative stereochemistry of compound **11** was deduced from bidimensional NMR experiments. Particularly, NOESY experiments showed unambiguous correlations between the co-facial protons.

Last attempts to form a tricyclic structure from the unactivated dienyne **8** were performed under catalytic conditions. In particular, using the Wender conditions ($RhCl(CO)(PPh_3)_2$–$AgSbF_6$ under CO atmosphere)[13a] or the Montgomery conditions ($Ni[Cod]_2$, $TMSCHN_2$ as the monocarbon entity)[13b] gave no trace of compounds resulting from the [4+2+1] cycloaddition. This could be explained by the constraints fixed by the substrate in regard to the cycloaddition mechanism.[13] These reactions have indeed been reported on linear dienynes only, which is not the case of compound **8**. Furthermore, no [4+2] cycloaddition arose when submitting **8** to $Ni(Cod)_2$ or $RhCl(CO)(PPh_3)_2$–$AgSbF_6$ under inert atmosphere.

In this Letter, we showed that model compound **9** can be used to generate highly strained cup-shaped molecules such as tricycle **11** under the thermal Diels–Alder conditions. Although numerous attempts were made for the synthesis of the cup-shaped 5/5/6-tricyclic structure, it was not possible to catalyze the cycloaddition of the unactivated dienyne **8**. Our work is pursued to develop strategies for the synthesis of complex polycyclic compounds.

Acknowledgement

L.E. thanks the MENRT for receipt of a research scholarship.

References and notes

1. For examples of 5/5/6-tricyclic natural products, see: (a) Bohlmann, F.; Ziesche, J.; Gupta, R. K. *Phytochemistry* **1982**, *21*, 1331–1334; (b) Melching, S.; König, W. A. *Phytochemistry* **1999**, *51*, 517–523; (c) Durán-Patrón, R.; Colmenares, A. J.; Hernándes-Galán, R.; Collado, I. G. *Tetrahedron* **2001**, *57*, 1929–1933.
2. For synthetic methods concerning 5/5/6-tricyclic systems, see: (a) Gibbard, H. C.; Moody, C. J.; Rees, C. W. *J. Chem. Soc., Perkin Trans. 1* **1985**, 731–735; (b) Haufe, R.; Jansen, M.; Tobias, K. M.; Winterfeldt, E.; Wray, V. *Chem. Ber.* **1987**, *120*, 2007–2013; (c) Mehta, G.; Subrahmaniyam, D. *J. Chem. Soc., Perkin Trans. 1* **1991**, 395–401; (d) Weyerstahl, P.; Marschall, H.; Schulze, M.; Schwope, I. *Liebigs Ann.* **1996**, 799–807; (e) Hicks, F. A.; Kablaoui, N. M.; Buchwald, S. L. *J. Am. Chem. Soc.* **1996**, *118*, 9450–9451; (f) Shankar, S.; Coates, R. M. *J. Org. Chem.* **1998**, *63*, 9177–9182; (g) Yeh, M.-C. P.; Tsao, W.-C.; Ho, J.-S.; Tai, C.-C.; Chiou, D.-Y.; Tu, L.-H. *Organometallics* **2004**, *23*, 792–799; (h) Funel, J.-A.; Prunet, J. *Synlett* **2005**, 235–238; (i) Krafft, M. E.; Kyne, G. M.; Hirosawa, C.; Schmidt, P.; Abboud, K. A.; L'Helias, N. *Tetrahedron* **2006**, *62*, 11782–11792.
3. Lee, A. H. F.; Chan, A. S. C.; Li, T. *Tetrahedron* **2003**, *59*, 833–839.
4. Cardillo, G.; Fabbroni, S.; Gentilucci, L.; Gianotti, M.; Tolomelli, A. *Synth. Commun.* **2003**, *33*, 1587–1594.
5. Enyne **5**: ^{1}H NMR (300 MHz, $CDCl_3$) δ ppm: 0.04 (s, 6H), 0.89 (s, 9H), 1.21–1.60 (m, 4H), 1.76 (t, *J* 2.6 Hz, 3H), 2.77 (m, 3H), 3.59 (m, 2H), 3.71 (s, 3H), 3.73 (s, 3H), 5.15 (dd, *J* 2.1 Hz, 15.8 Hz, 1H), 5.16 (dd, *J* 2.0 Hz, 13.1 Hz, 1H), 5.50 (m, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ ppm: −5.2 (2C), 3.4, 18.3, 24.6, 25.9, 26.7, 31.4, 47.7, 52.1, 52.3, 60.7, 63.1, 73.9, 78.5, 118.8, 136.7, 170.2, 170.4. IR (CH_2Cl_2) ν cm^{-1}: 1732 (C=O). HRMS (CI+, CH_4) *m*/*z*: calculated for $[C_{21}H_{37}O_5Si]^+$: 397.2410; found: 397.2406. R_f (toluene–ethanol 98:2): 0.6.
6. Diene **6**: ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm: 0.04 (s, 6H), 0.88 (s, 9H), 1.21 (m, 1H), 1.55 (m, 1H), 1.57 (m, 2H), 1.90 (s, 3H), 2.90 (d, *J* 16.3 Hz, 1H), 3.43 (dt, *J* 1.8 Hz, 16.3 Hz, 1H), 3.58 (m, 1H), 3.59 (dt, *J* 1.4 Hz, 6.3 Hz, 2H), 3.72 (s, 3H), 3.73 (s, 3H), 4.91 (s, 1H), 4.95 (s, 1H), 5.71 (s, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ ppm: −5.4 (2C), 18.3, 20.3, 25.9, 27.4, 30.9, 39.6, 50.3, 52.3, 52.7, 63.0, 63,4, 113.5, 128.1, 139.0, 140.7, 170.8, 172.7. IR (CH_2Cl_2) ν cm^{-1}: 1739 (C=O), 1669 (C=C). HRMS (CI+, CH_4) *m*/*z*: calculated for $[C_{21}H_{37}O_5Si]^+$: 397.2410; found: 397.2403. R_f (toluene–ethanol 98:2): 0.7.
7. Chatani, N.; Furukawa, N.; Sakurai, H.; Murai, S. *Organometallics* **1996**, *15*, 901–903.
8. (a) Mori, M.; Kitamura, T.; Sato, Y. *Synthesis* **2001**, 654–664; (b) Kinoshita, A.; Mori, M. *Synlett* **1994**, 1020–1022; (c) Evanno, L.; Nay, B.; Bodo, B. *Synth. Commun.* **2005**, *35*, 1559–1565.
9. Corey, E. J.; Fuchs, P. L. *Tetrahedron Lett.* **1972**, *36*, 3769–3772.
10. Tsuji, J.; Takahashi, M.; Takahashi, T. *Tetrahedron Lett.* **1980**, *21*, 849–850.
11. Dienyne **9**: ^{1}H NMR (300 MHz, $CDCl_3$) δ ppm: 1.53 (m, 1H), 1.77 (m, 1H), 1.91 (s, 3H), 2.42 (m, 2H), 2.94 (dt, *J* 1.1 Hz, 16.5 Hz, 1H), 3.40 (dt, *J* 1.9 Hz, 16.5 Hz, 1H), 3.67 (m, 1H), 3.75 (s, 3H), 3.76 (s, 3H), 3,76 (s, 3H), 4.93 (s, 1H), 4.98 (s 1H), 5.66 (s, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ ppm: 17.1, 20.2, 29.1, 39.8, 49.7, 52.5 (2C), 52.7, 63.3, 73.3, 86.6, 114.1, 126.4, 138.7, 141.8, 150.6, 170.5, 172.2. IR (CH_2Cl_2) ν cm^{-1}: 2241 (C≡C), 1731 (C=O), 1717 (C=O). R_f (cychohexane–ethyl acetate 7:3): 0.4.
12. Cycloadduct **11**: ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm: 1.16 (m, 1H), 1.78 (s, 3H), 2.04 (m, 1H), 2.48 (m, 1H), 2.63 (m, 1H), 2.81 (d, *J* 17.4 Hz, 1H), 3.20 (m, 3H), 3.27 (d, *J* 17.4 Hz, 1H), 3.45 (m, 1H), 3.70 (s, 3H), 3.74 (s, 3H), 3.76 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ ppm: 19.0, 29.9, 34.4, 35.6, 37.2, 47.1, 51.2, 52.3, 52.8, 55.0, 63.5, 128.8, 128.3, 133.9, 162.2, 167.2, 170.8, 173.0. IR (NaCl) ν cm^{-1}: 1728 and 1705 (C=O), 1636 (substituted C=C), 1269–1169 (C–O), 1072. HRMS (ESI+) *m*/*z*: calculated for $[C_{18}H_{23}O_6]^+$: 335.1495; found: 335.1488. R_f (cyclohexane–ethyl acetate 7:3): 0.6.
13. (a) Wender, P. A.; Deschamps, N. M.; Gamber, G. G. *Angew. Chem., Int. Ed.* **2003**, *42*, 1853–1857; (b) Ni, Y.; Montgomery, J. *J. Am. Chem. Soc.* **2006**, *128*, 2609–2614.