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Methoxyallene, a Building Block for the Synthesis of Seven-Membered Oxacycles

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Abstract: An efficient new approach for the synthesis of seven-membered oxacycles is described.

Interest in the synthesis of seven-membered oxacycles has steadily increased in recent years, mainly because of the occurrence of these substructures in a wide variety of bioactive natural products.[1]

From the monocyclic Zoapatanol[2] (fig 1) to the more complex polyether toxins such as ciguatoxin[3] or the brevetoxins,[4] these molecules represent challenging synthetic targets for the organic chemist.

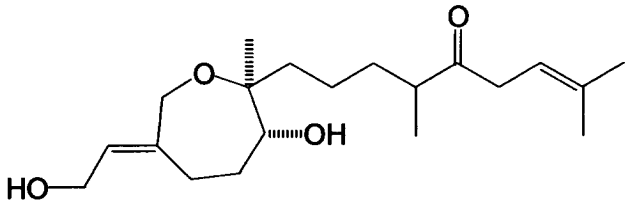

Figure 1. Zoapatanol

A recent review article [5] highlighting the different approaches in the literature to oxepanes and oxepenes prompted us to report our preliminary results on the subject (scheme 1). Propargylic alcohol **1** was *O*-methylated with dimethylsulphate to provide 3-methoxy-1-propyne (**2**).[6] Isomerization of **2** with potassium *tert*-butoxide afforded methoxyallene **3** in high yield.[7,8] Sequential metalation, alkylation, metalation and carboxylation of **3** afforded, after acidic work up,[9] butenolide **5** (78% from **3**). Deprotection of the TBS groups with TBAF afforded bicyclic seven-membered oxacycle **6**[10] in 63%, *via* an intramolecular Michael addition. (Compound **6** was obtained as a single isomer).

In conclusion we have developed a new and efficient methodology for the synthesis of oxepanes from readily available methoxyallene **3**. The application of this methodology to the synthesis of Zoapatanol and related natural products containing the oxepane or the oxepene units is in progress and will be reported in due course.

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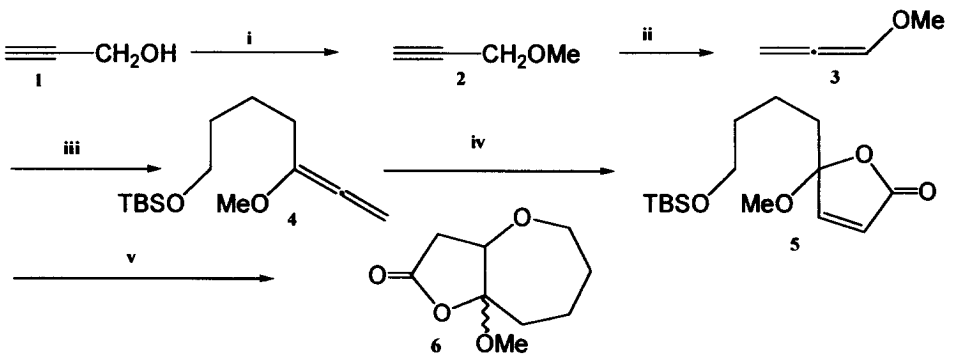

Scheme 1. Reaction conditions. (i) Me_2SO_4, NaOH (79%). (ii) *t*BuOK(10%) (78%). (iii) *n*BuLi/THF –30°C, $I(CH_2)_4OTBS$ (97%). (iv) *t*BuLi/THF, -70°C, 1h, CO_2; 10% H_2SO_4-Et_2O, 0°C, 1h (80%). (v) TBAF/THF, rt, 2h (63%).

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Referencies and Notes.

1. (a) Macias, F.A.; Molinillo, J. M. G.; Varela, R. M.; Torres, A.; Fronczek, F. R. *J. Org. Chem.* **1994**, *59*, 8261-8266. (b) Faulkner, D. *J. Nat. Prod. Rep.* **1996**, *13*, 75-125. (c) Marata, K.; Satake, M.; Naoki, H.; Kaspar, H. F.; Yasumoto, T. *Tetrahedron* **1998**, *54*, 735-742. (d) Hosokawa, S.; Isobe, M. *J. Org. Chem.* **1999**, *64*, 37-48.
2. (a) Trost, B. M.; Greenspan, P. D.; Geissler, H.; Kim, J.; Greeves, N. *Angew. Chem., Int. Ed. Engl.* **1994**, *33*, 2182-2184. (b) Kocienski, P. J.; Love, C.; Whitby, R.; Roberts, D. A. *Tetrahedron Lett.* **1988**, *29* 2867-2870.
3. Yasumoto, T.; Murata, M. *Chem. Rev.* **1993**, *93*, 1897-1909.
4. Nicolaou, K. C. *Angew. Chem.,Int. Ed. Engl.* **1996**, *35*, 589-607.
5. Hoberg, J. O. *Tetrahedron* **1998**, *54*, 12631-12670.
6. Reppe, W. *Liebigs Ann. Chem.* **1955**, 596.
7. Weiberth, F. J.; Hall, S. S. *J. Org. Chem.* **1985**, *50*, 5308-5314.
8. Zimmer, R. *Synthesis* **1993**, 165-178.
9. (a) Derguini, F.; Linstrumelle, G. *Tetrahedron Lett.* **1989**, 25, 5763. (b) Kocienski, P. J.; Fall, Y.; Whitby, R. *J. Chem. Soc., Perkin Trans 1.* **1989**, 841-844.
10. Selected data for **6**: **^{1}H NMR** (360 MHz, $CDCl_3$) d 4.17 (ddt, 1H, J = 11.7, 3.6 and 2.2 Hz), 3.92 (dd, 1H, J = 8 and 1.8 Hz), 3.31 (s, 3H), 3.02 (dd, 1H, J = 18.9 and 8 Hz), 2.46 (dd, 1H, J = 18.9 and 1.8 Hz), 2.39 (t, 1H, J = 8 Hz), 1.65-1.85 (5H, m), 1.4-1.5 (1H, m); **^{13}C NMR** (65 MHz, $CDCl_3$) d 174.38 (CO), 114.54(C),84.51(CH), 74.60(CH_2), 50.01(CH_3), 36.72(CH_2), 31.74(CH_2), 30.64(CH_2), 21.03(CH_2); MS(m/e): 155(M^+-CH_3O, 66%), 115(100), 99(3), 87(2), 83(38), 73(31), 67(4), 59(2), 55(21), 43(2).