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A synthetic approach to bicyclo[6.2.1]undecane ring systems

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Abstract—A synthesis of a functionalized bicyclo[6.2.1]undecane, *N*-(7-hydroxymethyl-bicyclo[6.2.1]undeca-3,5,9-trien-2-yl)-4-methyl-benzenesulfonamide, is described. Starting with a [6+4] cycloaddition between cyclopentadiene and cycloheptatrienone, the final product was prepared in five steps with an overall 37% yield. The remarkable resistance to hydrolysis of an intermediate lactam was overcome by tosylating the amide and reducing with $LiAlH_4$.

Bridged bicyclic systems are molecular features of considerable interest both under theoretical[1] or synthetic[2,3] points of view; the elaboration of efficient methods for constructing these structures has been a challenging task for the organic chemists. A particular system, bicyclo[6.2.1]undecane (**1**), has been the object of the efforts of many research groups in the last few decades, because this structure is a good precursor of natural products such as taxanes and their derivatives;[3] other natural products such as goyazensolide (**2**),[4a] eremantholide C (**3**),[4b] and many other furanoheliangolide sesquiterpenes,[5] also have in their core the bicyclo[6.2.1]undecane structure and their syntheses have been explored by different research groups (Fig. 1).[6–9]

Some of the reported syntheses are based on [3,3]-sigmatropic rearrangements;[3] the alternative approach starting with a cycloaddition ([4+2] or [6+4]) reaction followed by a cleavage of an internal bond of the polycyclic system[1a,10] is sometimes more efficient. In this paper we report a method to obtain the bicyclo[6.2.1]undecane structure from the adduct **6** that produces a functionalized bicyclic system (Scheme 1).

We found that the cycloaddition reaction produced a higher yield when carried out by heating (90°C) a benzene solution of the reagents for 19 h, starting with 2 equivalents of cyclopentadiene and adding another equivalent of the diene after 15 h (84% yield) (cf. method described by Itô and co-workers[11,16]). Ketone **6** was converted into the correspondent oxime **7** in 80% yield by the method described by Subba Rao and co-workers;[12,17] a Beckmann rearrangement[13,18] of **7** produced lactam **8** in 59% yield. Contrary to our expectations, lactam **8** could not be easily hydrolyzed; all attempts to promote hydrolysis or methanolysis of **8**

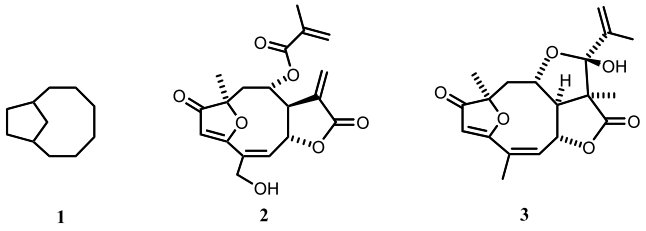
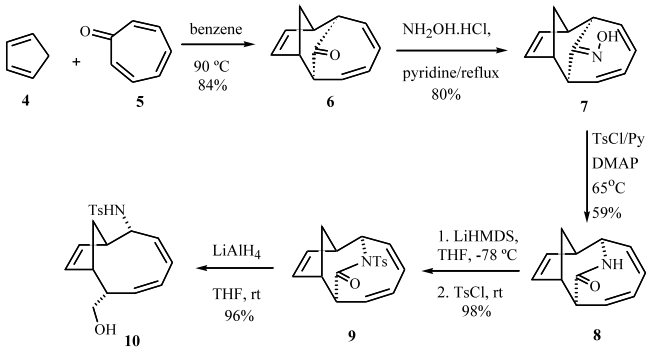


Figure 1.



Scheme 1.

Keywords: bicyclo[6.2.1]undecane ring; [6+4] addition reaction; lactam tosylation; Beckmann rearrangement.

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resulted either in recovery of starting materials or in a complex mixture of products. Treatment of **8** with $LiAlH_4$ also gave a complex mixture. We could overcome this problem by first tosylating lactam **8** through the method described by Heathcock and Griffith[14,19] (98% yield) and then reducing[15,20] **9** with $LiAlH_4$ (96% yield) thus obtaining the desired bicyclo[6.2.1]undecane structure in compound **10** with an overall yield of 37%.

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References

1. (a) Paquette, L. A.; Kukla, M. J.; Ley, S. V.; Traynor, S. G. *J. Am. Chem. Soc.* **1977**, *99*, 4756–4763; (b) Sakai, Y.; Toyotani, S.; Ohtani, M.; Matsumoto, M.; Tobe, Y.; Odaira, Y. *Bull. Chem. Soc. Jpn.* **1981**, *54*, 1474; (c) Mi, B.; Maleczka, R. E., Jr. *Tetrahedron Lett.* **1999**, *40*, 2053–2056.
2. (a) Leonard, N. J.; Little, J. C. *J. Am. Chem. Soc.* **1958**, *80*, 4111–4114; (b) Büchi, G.; Erickson, R. E.; Wakabayashi, N. *J. Am. Chem. Soc.* **1961**, *83*, 927–938; (c) Tobe, Y.; Fukuda, Y.; Kakiuchi, K.; Odaira, Y. *J. Org. Chem.* **1984**, *49*, 2012–2015; (d) Corbett, R. M.; Lee, C. S.; Sulikowski, M. M.; Reibenspies, J.; Sulikowski, G. A. *Tetrahedron* **1997**, *53*, 11099–11108.
3. (a) Paquette, L. A.; Pegg, N. A.; Toops, D.; Maynard, G. D.; Rogers, R. D. *J. Am. Chem. Soc.* **1990**, *112*, 277–283; (b) Paquette, L. A.; Bailey, S. *J. Org. Chem.* **1995**, *60*, 7849–7856; (c) Paquette, L. A.; Montgomery, F. J.; Wang, T. Z. *J. Org. Chem.* **1995**, *60*, 7857–7864; (d) Zeng, Q.; Bayley, S.; Wang, T. Z.; Paquette, L. A. *J. Org. Chem.* **1998**, *63*, 137–143; (e) Paquette, L. A.; Zeng, Q. *Tetrahedron Lett.* **1999**, *40*, 3823–3826.
4. (a) Vichnewski, W.; Takahashi, A. M.; Nasi, A. M. T.; Gonçalves, D. C. R.; Dias, D. A.; Lopes, J. N. C.; Goedken, V. L.; Gutiérrez, A. B.; Herz, W. *Phytochemistry* **1989**, *28*, 1441–1451; (b) Paquette, L. A. *Chem. Soc. Rev.* **1995**, 9–16.
5. Minnaard, A.; Wijnberg, J. B. P. A.; de Groot, A. *Tetrahedron* **1999**, *55*, 2115–2146.
6. Takao, K.; Ochiai, H.; Yoshida, K.; Hashizuka, T.; Koshimura, H.; Tadano, K.; Ogawa, S. *J. Org. Chem.* **1995**, *60*, 8179–8193.
7. Boeckman, R. K., Jr.; Yoon, S. K.; Heckendorn, D. K. *J. Am. Chem. Soc.* **1991**, *113*, 9682–9684.
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*, 91–97.
10. Constantino, M. G.; Beatriz, A.; da Silva, G. V. J. *Tetrahedron Lett.* **2000**, *41*, 7001–7004.
11. Itô, S. B.; Fujise, Y.; Okuda, T.; Inoue, Y. *Bull. Chem. Soc. Jpn.* **1966**, *39*, 1351.
12. Laxmisha, M. S.; Subba Rao, S. R. *Tetrahedron Lett.* **2000**, *41*, 3759–3761.
13. Grieco, P. A.; Flynn, D. L.; Zelle, R. E. *J. Am. Chem. Soc.* **1984**, *106*, 6414–6417.
14. Griffith, D. A.; Heathcock, C. H. *Tetrahedron Lett.* **1995**, *36*, 2381–2384.
15. Vandewalle, M.; Eycken, J. V.; Oppolzer, W.; Vullioud, C. *Tetrahedron* **1986**, *42*, 4035–4043.
16. Compound **6**: *tricyclo[4.4.1.1^{2,5}]dodeca-3,7,9-trien-11-one*: **^{1}H NMR** ($CDCl_3$, 500 MHz), δ (ppm): 1.53 (dtt, 1H, $J_1=11.5$ Hz, $J_2=J_3=4.9$ Hz, $J_4=J_5=1.3$ Hz); 2.29 (dquint, 1H, $J_1=11.5$ Hz, $J_2=J_3=J_4=J_5=0.9$ Hz); 3.05 (dddd, 2H, $J_1=4.9$; $J_2=3.3$, $J_4=2.2$, $J_5=0.9$ Hz); 3.24 (ddt, 2H, $J_1=7.0$, $J_2=2.2$, $J_3=J_4=0.9$); 5.69 (ddd, 2H, $J_1=9.1$ Hz, $J_2=7.0$ Hz, $J_3=3.0$ Hz); 5.95–6.08 (m, 4H). **^{13}C NMR**, ($CDCl_3$, 125 MHz), δ (ppm): 33.2 (CH_2); 48.6 (CH); 57.9 (CH); 126.9 (CH); 128.3 (CH); 135.5 (CH); 208.8 (C=O). **IR** ν_{max} (KBr), 1717, 3406 cm^{-1}. **MS** *m/z* (relative intensity) 172 [M$^+$] (5.3%), 128 (6.2%), 107 (100%), 79 (8.4%), 77 (19.2), 66 (48.0%), 51 (19.8%) 39 (41.3%). Mp 71–72°C.
17. Compound **7**: *tricyclo[4.4.1.1^{2,5}]dodeca-3,7,9-trien-11-one oxime*: **^{1}H NMR** ($CDCl_3$, 500 MHz), δ (ppm): 1.38 (dtt, 1H, $J_1=11.1$ Hz, $J_2=J_3=5.0$ Hz, $J_4=J_5=1.0$ Hz); 2.03 (dquint, 1H, $J_1=11.1$ Hz, $J_2=J_3=J_4=J_5=0.8$ Hz); 2.86–2.91 (m, 1H); 2.91–2.96 (m, 1H); 3.21 (dddd, 1H, $J_1=6.6$ Hz, $J_2=3.8$, $J_3=3.0$, $J_4=0.8$ Hz); 4.23 (ddt, 1H, $J_1=8.0$ Hz, $J_2=J_3=3.0$ Hz, $J_4=0.8$ Hz); 5.85–6.04 (m, 6H); 8.37 (sl, 1H). **^{13}C NMR** ($CDCl_3$, 125 MHz) δ (ppm): 33.8 (CH_2); 39.5 (CH); 45.7 (CH); 47.2 (CH); 47.7 (CH); 126.2 (CH); 127.5 (CH); 131.2 (CH); 133.3 (CH); 134.9 (CH); 135.0 (CH); 158.7 (C=NOH). **IR** ν_{max} (KBr): 1455, 2933, 3267 cm^{-1}. **MS** *m/z* (relative intensity): 187 [M$^+$] (6.3%), 170 [M$^+$–OH] (24%), 121 (93.4%), 104 (12%), 91 (14.8%), 78 (100%), 66 (14.1%), 39 (24.5%).
18. Compound **8**: *11-aza-tricyclo[4.4.2.1^{2,5}]trideca-3,7,9-trien-12-one*: **^{1}H NMR** ($CDCl_3$, 500 MHz), δ (ppm): 1.60 (dt, 1H, $J_1=12.1$ Hz, $J_2=J_3=6.3$ Hz); 2.25 (d, 1H, $J=12.1$ Hz); 2.99 (ddt, 2H, $J_1=J_2=6.3$ Hz, $J_3=2.9$ Hz, $J_4=1.7$ Hz); 3.64 (dddd, 1H, $J_1=9.6$ Hz, $J_2=6.3$ Hz, $J_3=2.0$ Hz, $J_4=1.0$ Hz); 3.81 (dt, $J_1=7.8$ Hz, $J_2=J_3=6.3$ Hz); 5.81 (dd, 1H, $J_1=5.9$ Hz, $J_2=2.9$ Hz); 5.95–6.09 (m, 4H); 6.10 (dd, 1H, $J_1=5.9$ Hz, $J_2=2.8$ Hz); 6.20–6.35 (sl, 1H). **^{13}C NMR** ($CDCl_3$, 125 MHz) δ: 33.9 (CH_2); 45.5 (CH); 47.9 (CH); 50.7 (CH); 53.8 (CH); 127.4 (CH); 128.3 (CH); 132.9 (CH); 133.5 (CH); 135.5 (CH); 137.5 (CH); 174.4 (C=O). **IR** ν_{max} (KBr): 1650, 2917, 3191 cm^{-1}. **MS** *m/z* (relative intensity): 187 [M$^+$] (7.5%), 93 (25.7%), 86 (46.5%), 84 (69.1%), 67 (25.3%), 51 (34.4%), 49 (100%), 35 (15.7%). Mp: 161–162°C.
19. Compound **9**: *11-(toluene-4-sulfonyl)-11-aza-tricyclo-[4.4.2.1^{2,5}]trideca-3,7,9-trien-12-one*: **^{1}H NMR** ($CDCl_3$, 500 MHz), δ (ppm): 1.63 (dddd, 1H, $J_1=12.3$ Hz, $J_2=6.9$ Hz, $J_3=5.8$ Hz, $J_4=1.7$ Hz); 2.23 (dt, 1H, $J_1=12.3$ Hz, $J_2=J_3=1.6$ Hz); 2.38 (s, 3H); 3.00 (ddd, 1H, $J_1=7.1$ Hz, $J_2=5.8$ Hz, $J_3=2.9$ Hz); 3.28 (dt, 1H, $J_1=J_2=6.9$ Hz, $J_3=3.0$ Hz); 3.68 (ddd, 1H, $J_1=10.3$ Hz, $J_2=7.1$ Hz, $J_3=1.7$ Hz); 5.41 (dd, 1H, $J_1=8.3$ Hz, $J_2=6.9$ Hz); 5.79 (dddd, 1H, $J_1=13.0$ Hz, $J_2=10.3$ Hz, $J_3=1.7$ Hz, $J_4=0.7$ Hz); 5.83 (ddd, 1H, $J_1=5.7$ Hz, $J_2=3.0$ Hz, $J_3=1.6$ Hz); 6.03 (ddd, 1H, $J_1=13.0$ Hz, $J_2=8.7$ Hz, $J_3=0.8$ Hz); 6.07 (ddd, 1H, $J_1=5.7$ Hz,

$J_2=2.9$ Hz, $J_3=1.6$ Hz); 6.16 (ddd, 1H, $J_1=12.6$ Hz, $J_2=8.7$ Hz, $J_3=0.7$ Hz); 6.26 (dddd, 1H, $J_1=12.6$ Hz, $J_2=8.3$ Hz, $J_3=1.7$ Hz, $J_4=0.8$ Hz); 7.23 (d, 2H, $J=8.1$ Hz); 7.71 (d, 2H, $J=8.1$ Hz). **^{13}C NMR** ($CDCl_3$, 125 MHz) δ (ppm): 21.6 (CH_3); 33.2 (CH_2); 45.2 (CH); 47.2 (CH); 52.6 (CH); 55.3 (CH); 128.2 (CH); 128.4 (CH); 128.6 (CH); 128.9 (CH); 130.9 (CH); 132.0 (CH); 136.0 (CH); 136.1 (CH); 136.4 (CH); 144.0 (CH); 171.2 (C=O). **IR** ν_{max} (KBr): 1162, 1675, 2993, 3009, 3358 cm^{-1}. **MS** m/z (relative intensity): 186 [M$^+$–Ts] (54.7%), 155 (21.3%), 120 (49.6%), 91 (100%), 66 (47.9%), 65 (92%), 39 (68.6%). Mp: 214–215°C.

20. Compound **10**: *N-(7-hydroxymethyl-bicyclo[6.2.1]undeca-3,5,9-trien-2-yl)-4-methyl-benzenesulfonamide*: **^{1}H NMR** ($CDCl_3$, 500 MHz), δ (ppm): 1.74 (ddd, 1H, $J_1=13.9$ Hz, $J_2=1.0$, $J_3=0.8$); 1.90 (sl, 1H); 2.06 (dt, 1H, $J_1=13.9$; $J_2=J_3=9.5$ Hz); 2.29 (dddt, 1H, $J_1=8.8$ Hz, $J_2=J_3=7.1$ Hz, $J_4=2.5$ Hz, $J_5=0.9$ Hz); 2.41 (s, 3H); 2.73 (dddd, 1H, $J_1=9.5$ Hz, $J_2=3.2$ Hz, $J_3=2.5$ Hz, $J_4=1.0$ Hz); 3.17 (tddd, 1H, $J_1=J_2=9.5$ Hz, $J_3=3.0$ Hz, $J_4=1.3$ Hz, $J_5=0.8$ Hz); 3.56 (d, 2H, $J=7.1$ Hz); 4.19 (dt, 1H, $J_1=J_2=9.5$, $J_3=8.1$ Hz); 4.89 (d, 1H, $J=9.5$ Hz); 5.32 (dddd, 1H, $J_1=11.3$ Hz, $J_2=8.8$ Hz, $J_3=2.0$ Hz, $J_4=0.8$ Hz); 5.53 (dddd, 1H, $J_1=11.6$ Hz; $J_2=8.1$ Hz, $J_3=1.8$ Hz, $J_4=0.8$ Hz); 5.66 (dddt, 1H, $J_1=5.5$ Hz; $J_2=3.0$ Hz, $J_3=2.0$ Hz, $J_4=0.8$ Hz); 5.76 (ddd, 1H, $J_1=5.5$ Hz, $J_2=3.2$ Hz, $J_3=1.3$ Hz); 5.81 (ddd, 1H, $J_1=11.6$ Hz; $J_2=2.0$ Hz, $J_3=1.8$ Hz); 5.97 (dddd, 1H, $J_1=11.3$ Hz, $J_2=2.0$ Hz, $J_3=1.8$ Hz, $J_4=0.9$ Hz); 7.26 (d, 2H, $J=8.3$ Hz); 7.70 (d, 2H, $J=8.3$ Hz). ^{13}C NMR ($CDCl_3$, 125 MHz) δ (ppm): 21.4 (CH_3); 34.6 (CH_2); 45.0 (CH); 46.3 (CH); 47.2 (CH); 53.2 (CH); 66.0 (CH_2); 127.0 (CH); 128.4 (CH); 128.7 (CH); 129.4 (CH); 131.6 (CH); 133.6 (CH); 134.9 (CH); 135.0 (CH); 138.1 (C); 143.1 (C). **IR** ν_{max} (KBr): 680; 730; 1154; 1328; 2600–3700 cm^{-1}. **MS** m/z (relative intensity): 279 (34.4%), 124 (18.9%), 106 (53%), 91 (100%), 80 (69.9%), 66 (36.1%), 43 (40.8%), 39 (32%).