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A Concise Entry into the Bicyclo[6.4.0]dodecane System Present in Taxanes. Regioselective Haller-Bauer Cleavage in Tricyclo[8.2.1.$0^{2,9}$]tridecan-13-ones

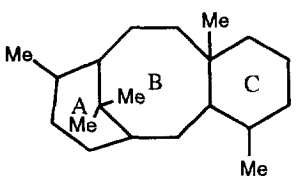
Goverdhan Mehta,* K. Subba Reddy
School of Chemistry, University of Hyderabad, Hyderabad 500 046, India

and

Ajit C. Kunwar*
Indian Institute of Chemical Technology, Hyderabad 500 007, India

Abstract: A short, regio- and stereoselective approach to functionalized *cis*-bicyclo[6.4.0]dodecane ring system from readily available 1,5-dimethyl-1,5-cyclooctadiene is reported.

Many recently discovered natural products are either entirely based on a bicyclo[6.4.0]dodecane skeleton or embody this framework as a significant part of their more complex molecular architecture. A celebrated example of the latter is the presence of the bicyclo[6.4.0]dodecane moiety as the BC-ring portion of the taxane skeleton **1**. As part of the intense world-wide interest in the synthesis of taxane-based diterpenoids and the anti-cancer drug paclitaxel in particular, several strategies have been developed for the construction of the 8-6 fused ring system in the past few years.[1] We have considered an approach to the taxane system **1**, in which the commercially available isoprene dimer (1,5-dimethyl-1,5-cyclooctadiene **2**)[2], constituting the B-ring and half the carbon content of **1**, could serve as the starting point. It was our intent to exploit each of the two transannularly disposed double bonds in **2** to append rings A and C enroute to **1** as shown in **3**. Towards this objective, we report herein on the six-membered ring annulation of **2** to deliver the BC ring fragment of **1** employing a Diels-Alder cycloaddition and a regioselective Haller-Bauer cleavage[3] as the key steps.



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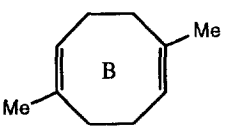

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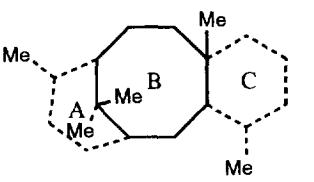

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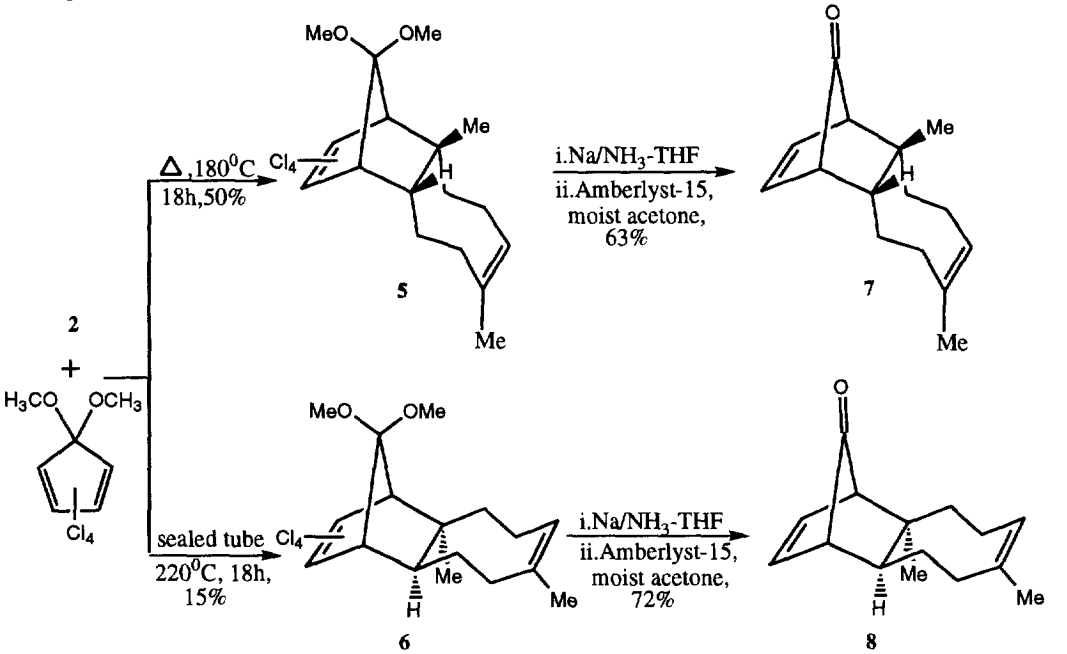
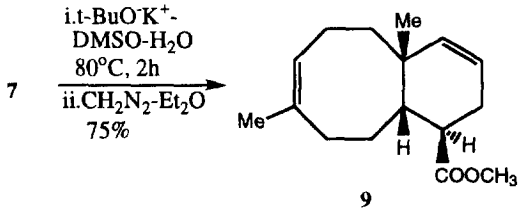
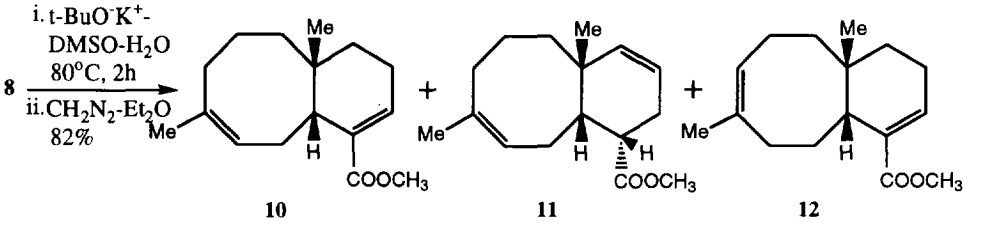
Diels-Alder reaction (reflux, 180°C) between **2** and 5,5-dimethoxy,1,2,3,4-tetrachlorocyclopentadiene **4** and column chromatography (SiO_2-gel) led to the isolation of a 1:1 tricyclic *endo*-adduct **5** (50%). However, when the Diels-Alder reaction was performed in a sealed tube at elevated temperature (220°C), considerable polymerization was encountered and a new 1:1 adduct, the tricyclic *exo*-adduct **6**, was isolated (15%). The diastereomeric nature of the two adducts (**5** and **6**) was revealed

when *endo*-**5** on heating in a sealed tube (210-220°C) was transformed to the thermodynamically more stable *exo*-**6** (70%). The ^1H and ^{13}C NMR spectra of **5** and **6** established their stereostructures. In the *endo*-adduct **5**, the quaternary methyl resonance appeared at δ 1.52, significantly deshielded by the spatially proximate ketal oxygen functionality. In the *exo*-adduct **6**, the quaternary methyl resonance was in the expected range (δ 1.21). Reductive dechlorination in **5** and deketalization furnished the tricyclic *endo*-dienone **7** in decent yield. Similar sequence with **6** led to the *exo*-dienone **8**. The quaternary methyl resonances in the ^1H NMR spectra of **7** and **8** were at δ 1.22 and 1.05, respectively, and further indicated that the abnormal deshielding in **5** was on account of the ketal group which was no longer present.



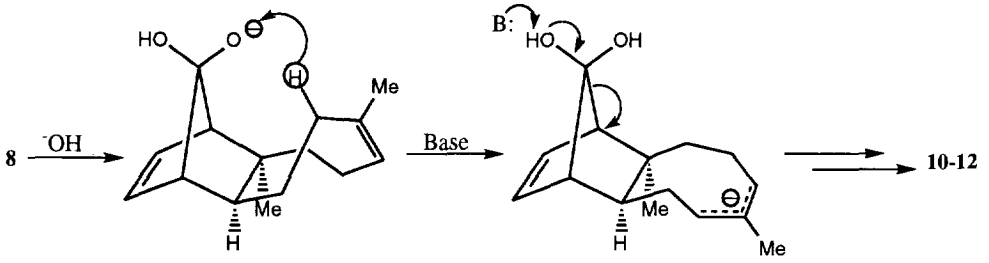
The *endo*-dienone **7** on exposure to K^+t-BuO^--DMSO-H_2O milieu, according to the procedure described by Gassman *et al.*[4] for the Haller-Bauer cleavage of non-enolizable ketones and esterification (CH_2N_2) furnished the *cis*-bicyclic diene ester **9** (75%) after purification (SiO_2-gel column). Under identical conditions,the *exo*-tricyclic dienone **8** gave the *cis*-diene esters **10-12** (~3:2:1, 82%) and these were separated by careful chromatography (SiO_2-gel). The elucidation of stereostructures of **9-12** required recourse to extensive high field ^1H NMR studies (TOCSY, DQF-COSY and NOESY) and led to the assignment of all the protons and identification of various spin networks.[5]





There are two features of this ready access to *cis*-bicyclo[6.4.0]dodecanes **9-12** that deserve further comments. Firstly, the base induced Haller-Bauer cleavage of tricyclic ketones **7** and **8** occur in a regioselective manner with the C-C bond scission exclusively taking place next to the quaternary carbon center bearing the methyl group. This regioselectivity ensured that the substituents on the derived bicyclic carbon framework are appropriately located as required for the BC rings of taxane. Secondly, it was quite intriguing to find that the double bond in the 8-membered ring had shifted in the products **10-11**, derived from the *exo*-**8**. Such a migration was not encountered in the *endo*-series. Since the products **10-12** were formed under equilibrating conditions and were found to be stable under the reaction conditions, it is tempting to speculate that the double bond migration takes place through an intramolecular hydrogen abstraction, prior to the Haller-Bauer cleavage as shown in the Scheme. The conformationally flexible 8-membered ring readily provides the latitude for such an intramolecular process, Scheme.

Scheme:



In conclusion, we have outlined a new, short and efficient strategy to *cis*-bicyclo[6.4.0]dodecane derivatives which correspond to the BC-ring portion of taxanes and are endowed with adequate functionalization in both the rings for further elaboration.

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References

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2. For use of **2** in synthesis see: (a) Mehta, G.; Rao, K.S.; *J. Am. Chem. Soc.*, **1986**, *108*, 8015. (b) Friedrich, D.; Paquette, L.A. *J. Chem. Soc. Perkin Trans.1*, **1991**, 1621.
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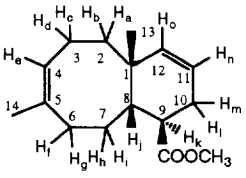
4. Gassman, P.G.; Lumb, J.T.; Zalar, F.V. *J. Am. Chem. Soc.*, **1967**, *89*, 946.

5. **9**: FAB MS $[M+H]^+$ 248; ^1H NMR (400 MHz, C_6D_6): δ 5.44 (ddd, 1H, J=10.0, 3.9, 3.5Hz, H_n), 5.36 (t, 1H, J=5.8Hz, H_e), 5.21 (ddd, 1H, J=10.0, 2.3, 2.0Hz, H_o), 3.35 (s, 3H, C9-COOC<u>H</u>3), 2.75 (ddd, 1H, J=8.5, 7.2, 6.3Hz, H_k), 2.44 (dddd, J=17.7, 7.2, 3.5, 2.3Hz, H_m), 2.31 (ddd, 1H, J=8.5, 7.2, 3.9Hz, H_j), 2.24 (ddd, 1H, J=14.9, 8.5, 6.2Hz, H_f), 2.08 (m, 2H, H_c and H_a), 2.03 (dd, 1H, J=14.9, 6.3Hz, H_g), 2.03 (dddd, 1H, J=17.7, 6.3, 3.9, 2.3Hz, H_l), 1.86 (m, 1H, J=14.7, 7.2, 6.9Hz, H_h), 1.75 (ddd, 1H, J=15.0, 8.9, 5.3Hz, H_d), 1.68 (br s, 3H, C_5-C<u>H</u>3), 1.67 (m, 1H, J=14.7, 8.5, 6.3Hz, H_i), 1.39 (ddd, 1H, J=15.0, 6.9, 4.6Hz, H_b), 0.99 (s, 3H, C_1-C<u>H</u>3); ^{13}C NMR (100 MHz, C_6D_6): δ 177.07, 139.06, 135.73, 124.14, 121.37, 51.38, 42.99, 42.35, 38.38, 38.01, 29.43, 27.95,



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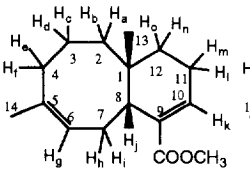

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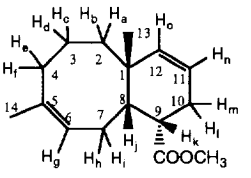

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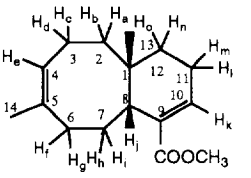

12

27.29, 27.21, 26.27, 24.75. **10**: FAB MS: $[M+H]^+$ 248; ^1H NMR (400 MHz, $CDCl_3$): δ 6.89 (t, 1H, J=3.8Hz, H_k), 5.36 (t, 1H, J=5.8Hz, H_g), 3.73 (s, 3H, C9-COOC<u>H</u>3), 2.79 (br d, 1H, J=9.4Hz, H_j), 2.50 (ddd, 1H, J=13.7, 10.9, 5.4Hz, H_a), 2.15 (dddd, 1H, J=19.0, 6.1, 3.5, 2.0Hz, H_l), 2.12 (br m, 1H, H_i), 2.10 (dddd, 1H, J=19.8, 7.0, 4.10, 2.6Hz, H_m), 2.03 (dd, 1H, J=9.4, 5.7Hz, H_h), 1.97 (dt, 1H, J=13.7, 5.3Hz, H_b), 1.68 (br s, 3H, C_5-C<u>H</u>3), 1.68 (m, 1H, J=5.4, 5.3Hz, H_d), 1.64 (br m, 1H H_o), 1.58 (br m, 1H, H_e), 1.56 (br m, 1H, H_c), 1.38 (br s, 1H, H_f), 1.08 (dd, 1H, J=13.3, 6.1Hz, H_n), 0.85 (s, 3H, C_1-C<u>H</u>3); ^{13}C NMR (50 MHz, $CDCl_3$): δ 168.26, 138.18, 134.56, 133.93, 124.39, 51.51(2C), 42.20, 37.61, 35.23, 33.23, 30.64, 28.77, 25.83, 23.27, 23.18. **11**: ^1H NMR (400 MHz, $CDCl_3$): δ 5.55 (ddd, 1H, J=5.2, 2.2Hz, H_n), 5.36 (t, 1H, J=5.7Hz, H_g), 5.20 (ddd, 1H, J=10.1, 2.7, 1.6Hz, H_o), 3.70 (s, 3H, C9-COOC<u>H</u>3), 2.86 (ddd, 1H, J=11.8, 5.6, 3.2Hz, H_k), 2.60 (br d, 1H, J=11.2Hz, H_j), 2.50 (br dt, 1H, J=13.0, 4.4Hz, H_f), 2.21 (dddd, 1H, J=18.3, 11.8, 2.7, 2.2Hz, H_l), 2.15 (br m, 1H, H_i), 2.08 (dddd, 1H, J=18.3, 5.6, 5.2, 1.6Hz, H_m), 1.90 (ddd, 1H, J=14.4, 5.6, 3.5Hz, H_e), 1.72 (br m, 1H, H_h), 1.70 (m, 1H, H_d), 1.68 (br s, 3H, C_5-C<u>H</u>3), 1.68 (m, 1H, H_a), 1.55 (m, 1H, H_c), 1.28 (m, 1H, H_b), 1.14 (s, 3H, C_1-C<u>H</u>3); ^{13}C NMR (50.0 MHz, $CDCl_3$): δ 175.87, 136.69, 132.83, 124.09, 122.72, 51.61, 41.68, 41.48, 39.55, 36.01, 30.35, 28.11(2C), 26.82, 23.29, 22.80. **12:** ^1H NMR (400 MHz, C_6D_6): δ 6.73 (dd, 1H, J=4.3, 3.5Hz, H_k), 5.46 (t, 1H, J=8Hz, H_e), 3.40 (s, 3H, C9-COOC<u>H</u>3), 2.17 (br m, 1H, H_c), 1.94 (br m, 1H, H_d), 1.84 (ddt, 1H, J=19.5, 6.2, 4.3Hz, H_l), 1.82 (br m, 1H, H_a), 1.77 (dddd, 1H, J=19.5, 7.8, 6.2, 3.5Hz, H_m), 1.61 (br s, 3H, C_5-C<u>H</u>3), 1.46 (s, 3H, C_1-C<u>H</u>3), 1.43 (br m, 1H, H_n), 1.42 (br m, 1H, H_b), 1.35 (br m, 1H, H_o). For the protons (f-j) definite assignments could not be made. δ 2.24 (br m, 1H), 2.04 (dd, 1H, J=11.3, 5.5Hz), 1.84 (br m, 1H), 1.80 (br m, 1H), 1.57 (ddd, 1H, J=12, 6.5, 5.5Hz); ^{13}C NMR (50.0 MHz, $CDCl_3$): δ 160.49, 139.96, 137.5, 136.70, 123.63, 51.4, 45.33, 39.81, 30.98, 30.49, 30.37, 25.10, 24.73, 24.24(2C), 24.11.

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