

Synthesis of 5-hydroxy-4-methoxytricyclo[7.3.1.0^{2,7}]trideca-2,4,6-trien-8-one – precursor of putative bioisosteric colchicine analogues

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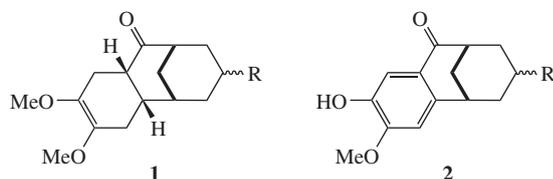
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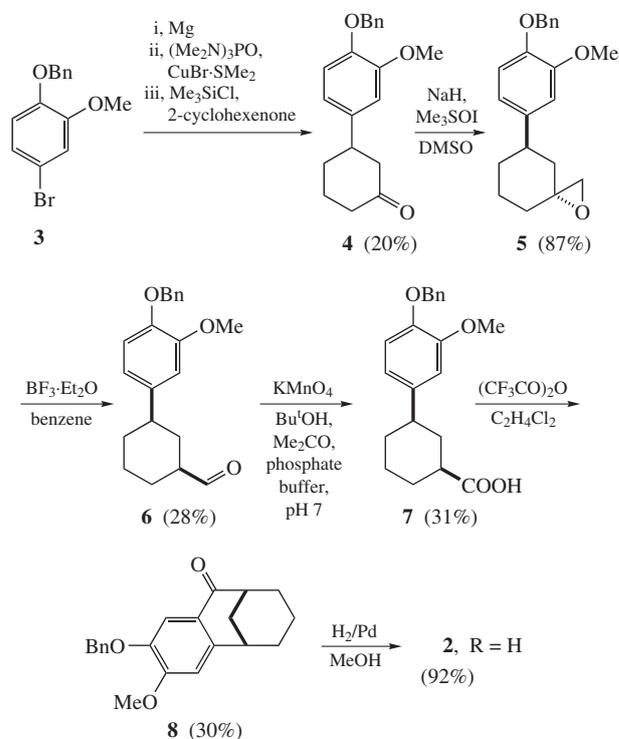
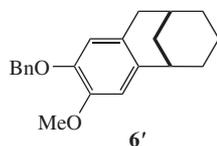
5-Hydroxy-4-methoxytricyclo[7.3.1.0^{2,7}]trideca-2,4,6-trien-8-one was synthesized from 1-benzyloxy-4-bromo-2-methoxybenzene in six steps comprising Corey–Chaykovsky epoxidation and Friedel–Crafts intramolecular cyclization. The crystal structure of the benzyl-protected derivative of the target compound was determined by X-ray analysis.

Last decade we were involved in the design and synthesis of physiologically active compounds with bridged and caged fragments (see, *e.g.*, refs. 1–8). We studied, in particular, the application of bridged groups for bioisosteric replacement of polycyclic cores of antitumour compounds taxol⁹ and colchicine.¹⁰ Based on the molecular modeling data, bicyclo[3.3.1]nonane derivatives **1** and **2** (R is ester, alkyl or alcohol moieties) were suggested as putative ligands of colchicine binding site in cell protein tubulin. However, the access to structural template **1** by the Diels–Alder reaction strategy was not successful.¹⁰ Herein, we report the synthesis of close in structure representative template **2** with R = H.



The target compound was synthesized in six steps (Scheme 1) from 1-benzyloxy-4-bromo-2-methoxybenzene **3** (obtained in two steps from guaiacol^{11,12}). Copper-catalyzed conjugate addition¹³ of arylmagnesium bromide obtained from **3** to 2-cyclohexenone gave product **4**. In the ¹H NMR spectrum of compound **4**, the axial proton at the C³ atom of the cyclohexane ring resonates as triplet of triplets at 2.97 ppm (1H) with H–H coupling constant ³J 11.6 Hz. Ketone **4** was subjected to the Corey–Chaykovsky epoxidation with dimethylsulfoxonium methylide generated *in situ* from trimethylsulfoxonium iodide in the presence of sodium hydride¹⁴ to afford oxirane **5** as individual diastereomer in a high yield. The appearance of the signals of two additional (in comparison with **4**) aliphatic protons in the area of 2.60–2.80 ppm in ¹H NMR spectrum of **5** and the additional resonance of the carbon atom at 53.98 ppm in ¹³C NMR spectrum proves the formation of the oxirane fragment. The product was assigned *trans*-configuration in compliance with the previous studies.¹⁵

The BF₃-assisted opening of epoxide in **5** gave aldehyde **6** as *cis*-isomer (the signal of the aldehyde proton in ¹H NMR



Scheme 1

spectrum is observed at 9.67 ppm, ³J of the multiplets of H¹ and H³ cyclohexyl protons are 11.9 and 13.4 Hz, respectively). Low isolated yield of compound **6** was due to the numerous reaction by-products one of which was separated and characterized as compound **6'** (two singlets of annelated aryl protons are observed at 6.62 and 6.72 ppm in ¹H NMR spectrum, whereas ¹³C NMR spectrum comprises seven signals of alicyclic carbon atoms).

Literature survey gave no examples of similar intramolecular cyclization joint with auto reduction for aryl-substituted epoxides, so this reaction is the subject of our further detailed studies.

The following oxidation of compound **6** to a corresponding acid met some difficulties. An attempt to apply Oxone oxidizing agent was not successful, while the use of freshly prepared Ag₂O afforded acid **7** in a very low yield (11%). Only the treatment of aldehyde **6** with KMnO₄ at neutral pH gave carboxylic acid **7** in acceptable yield of 31% (the carboxylic group is displayed as a resonance at 181.82 ppm in ¹³C NMR spectrum of **7**).

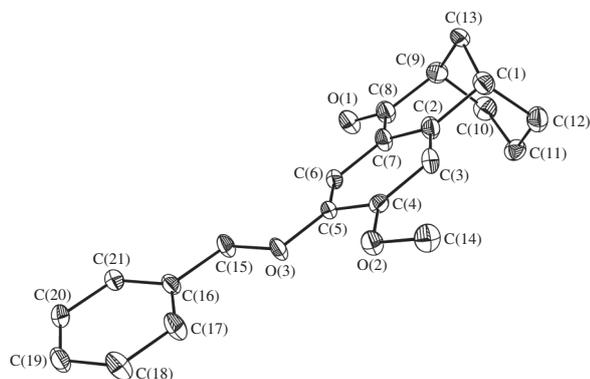


Figure 1 The general view of 5-benzyloxy-4-methoxytricyclo[7.3.1.0^{2,7}]-trideca-2,4,6-trien-8-one **8** in representation of atoms by thermal ellipsoids ($p = 50\%$).

The Friedel–Crafts intramolecular cyclization¹⁶ was performed for compound **7** to afford bicyclo[3.3.1]nonanone, annelated with the aromatic core, **8**. The structure of compound **8** was unambiguously proved by X-ray diffraction analysis.[†] According to these data (Figure 1), the six-membered ring C(1)–C(13)–C(9)–C(10)–C(11)–C(12) of the bicyclic fragment has Zefirov–Palyulin (ZP) and Cremer–Pople (CP) puckering parameters (calculated by RICON program¹⁷) $S_2 = 0.085$, $\theta = 4.2^\circ$, $\psi_2 = 22.0^\circ$, $\sigma = 0.33$ (ZP) and $Q = 0.587$, $\theta = 8.6^\circ$, $\varphi_2 = 21.4^\circ$ (CP), which correspond to the slightly distorted chair conformation. The ring C(1)–C(2)–C(7)–C(8)–C(9)–C(13) is strongly flattened (ZP: $S_2 = 0.501$, $\theta = 38.8^\circ$, $\psi_2 = 3.7^\circ$, $\sigma = 0.79$; CP: $Q = 0.534$, $\theta = 54.1^\circ$, $\varphi_2 = 3.3^\circ$) and adopts a conformation of slightly distorted envelope.

Deprotection of compound **8** led to the target compound **2** in a 92% yield. The spectral and elemental analysis prove the structure of ketone **2** ($R = H$).

In summary, a six-step scheme for constructing 5-hydroxy-4-methoxytricyclo[7.3.1.0^{2,7}]trideca-2,4,6-trien-8-one skeleton

[†] *Crystallographic data.* Crystals of **8** ($C_{21}H_{22}O_3$, $M = 322.39$, from CH_2Cl_2) are tetragonal, space group $I4_1/a$, at 100(2) K: $a = 18.6581(16)$, $b = 18.6581(16)$ and $c = 19.0674(17)$ Å, $V = 6637.8(10)$ Å³, $Z = 16$, $d_{calc} = 1.290$ g cm⁻³, $\mu(\text{MoK}\alpha) = 0.085$ cm⁻¹. Intensities of 35 250 reflections were measured with Bruker APEX-II CCD [$\lambda(\text{MoK}\alpha) = 0.71073$ Å, $2\theta < 58^\circ$] and 3820 independent reflections were used in the further refinement. The structure was solved by direct method and refined by the full-matrix least-squares technique against F^2 in the anisotropic–isotropic approximation. The refinement converged to $wR_2 = 0.1567$ and GOF = 1.042 for all independent reflections [$R_1 = 0.0561$ was calculated against F for 3114 observed reflections with $I > 2\sigma(I)$]. All calculations were performed using SHELXTL PLUS 5.1.

CCDC 992187 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via <http://www.ccdc.cam.ac.uk>. For details, see ‘Notice to Authors’, *Mendeleev Commun.*, Issue 1, 2014.

using Corey–Chaykovsky epoxidation and Friedel–Crafts intramolecular cyclization was elaborated. The scheme is useful for the further synthesis of putative ligands of colchicine binding site in β -tubulin, which is now in progress and will be published in due course.

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Online Supplementary Materials

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.mencom.2014.11.021.

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