New Approach to Bicyclo[5.3.0]decanes: Stereoselective Guaiane Synthesis

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ABSTRACT

A conceptually new and highly versatile approach to bicyclo[5.3.0]decanes, based on dichloroketene cycloaddition–diazooalkane ring expansion, is disclosed, and its relevance to natural product synthesis is demonstrated through the preparation of three guaiane sesquiterpenes. A concise total synthesis of a guaian-8,12-olide, 6-deoxygeigerin, highlights the effectiveness of the new methodology.

The bicyclo[5.3.0]decane ring system is present in numerous classes of sesquiterpenes (e.g., the guaianes, africananes, carotanes, lactaranes, and aromadendranes) and diterpenes (e.g., the daphanes, rhamnofolanes, sphaeroanes, tiglianes, and recently isolated guanacastepanes).1 The biological activity and structural complexity of the various bicyclo[5.3.0]decane natural products have combined to produce considerable synthetic effort, albeit often of limited breadth, over the past several decades.2 Herein, we disclose a conceptually new and highly versatile approach to bicyclo[5.3.0]decanes and demonstrate its relevance to natural product synthesis through the preparation of three guaiane sesquiterpenes. A concise total synthesis of a guaian-8,12-olide highlights our effort.

Readily available 7-methylcycloheptatriene 3 (I, Scheme 1) in the presence of dichloroketene was earlier found to yield regio- and stereoselectively α,α-dichlorocyclobutanone 2 (dr = 32:1).4 This cycloadduct has now been found to undergo regioselective ring expansion with diazomethane5a to afford, following dehydrochlorination,5b hydroazulenone 3 in 44% overall yield from 1 (76% yield per step).


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Significantly, other cycloheptatrienes\(^1\) (e.g., \(H, i-C_3H_7, C_6H_5\) replace \(CH_3\) in 1) and other diazoalkanes (e.g., \(CH_3CHN_2\)) have also been used in this sequence and with comparable efficiency.

This easily available, well-functionalized bicyclo[5.3.0]-decane offers a wide range of synthetic options, which can be expected to translate into a variety of rapid and efficient natural product syntheses (Scheme 2). For example, dehydrogenation/acetylation of 3 can be accomplished to yield azulene \(4\).\(^4\) For selective manipulation of the \(\alpha\)-chlorocyclopentenone portion of 3, the tricarbonyliron complexes 5 can be readily generated through treatment with \(Fe_2(CO)_9\) (5a,\(\beta\)-Fe(CO)\(_3\)). Further possibilities arise from the highly selective and efficient epoxidations that can be achieved at the distal unsaturation in 3: \(m\)-CPBA gives the \(\beta\)-epoxide 6\(^7\) (dr = 9:1), while NBS–LiH produces in good yield the \(\alpha\)-epoxide 7 (dr = 12:1) via the bromohydrin. The regioselectivity is different, however, in cycloaddition with Danishefsky’s diene, which affords as the major product the highly functionalized tricycle 8, possessing the 5–7–6 ring system common to the daphnanes, rhamnolofanes, sphaeroanes, and tiglianes.

Finally, and perhaps most importantly, conjugate addition to trienone 3 proceeds with remarkable stereo- and regioselectivity to yield the \(\beta\),1,6 adducts. For example, conjugate addition with K-Selectride, isopropenylmagnesium bromide, and the tert-butylimidethylsilyl ketene acetal from methyl propionate\(^8\) selectively provides adducts 9a–c,\(^7\) respectively. The C-7-substituted unsaturated adducts 9b,c,\(^7\) are particularly attractive precursors for accessing various guaianes and pseudoguaianes, especially guaianolides and pseudoguaianolides (vide infra).

The high degree of regioselectivity in the transformations that lead to 6–8 and 9a–c can be explained, at least in part, by limited conjugation of the C8,C9 double bond in the trienone system of 3. This rationale is supported by the

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**Scheme 2**

\(5a, \alpha\)-Fe(CO)\(_3\) \(\rightarrow\) 5b, \(\beta\)-Fe(CO)\(_3\) \(\rightarrow\) 7

\(\alpha\) Reaction conditions: (a) Pd(0), (CH\(_3\)CO\(_2\))\(_2\)O, C\(_6\)H\(_5\)CH\(_2\), 120 °C, 50%. (b) \(Fe_2(CO)_9\), (C\(_2\)H\(_5\))\(_2\)O, reflux, 76% (93% brsm). (c) \(m\)-CPBA, CH\(_2\)Cl\(_2\), 97%. (d) NBS, THF–H\(_2\)O; LiH, DMF, 79% (two steps). (e) CH\(_3\)=C(O(TMS)CH=CH(CH\(_3\))\(_2\), C\(_6\)H\(_5\)CH\(_2\), 180 °C, 31%. (f) 9a: K-Selectride, THF-DMPU, –80 to –40 °C, 67%. 9b: BrMgC\(_2\)H\(_4\)=CH\(_2\), CuBr-DMS, TMSCl, THF, –80 °C, 45% (dr ≥ 10:1). 9c: CH\(_3\)=CH=C(O(TBDMS)(O)CH\(_3\)), LiClO\(_4\), CH\(_3\)Cl\(_2\), 79% (dr = 6:1). brsm = based on recovered starting material.

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**Scheme 3**

\(9b \rightarrow 10a, X = \cdot\) \(\rightarrow\) 14a, \(X = \cdot\), \(R = CH_2OH\) \(\rightarrow\) 15a, 11-Epi-6-deoxygeigerin (\(\gg\)-CH\(_3\))

\(\alpha\) Reaction conditions: (a) (HOCH\(_2\))\(_2\)C(CH\(_3\))\(_2\), (CH\(_3\)O)\(_3\)CH, 101, 4003–4005. (b) Pd(0), (CH\(_3\)CO\(_2\))\(_2\)O, C\(_6\)H\(_5\)CH\(_2\), 120 °C, 50%. (c) \(Fe_2(CO)_9\), (C\(_2\)H\(_5\))\(_2\)O, reflux, 76% (93% brsm). N,N-Dimethyl-1-naphthylamine, Li, THF, –80 °C, then CH\(_3\)I, –80 to 20 °C, 93%. (b) 10% HCl, THF, quant. (c) Hg(OOC\(_2\)CF\(_3\))\(_2\), THF–H\(_2\)O, then NaOH, NaBH\(_4\), H\(_2\), THF-DMS, 55% (two steps). (d) KOH, CH\(_3\)OH, 46% (92% brsm). (e) (CH\(_3\)CO\(_2\))\(_2\)O, CF\(_3\)SO\(_2\)TMS, CH\(_2\)Cl\(_2\), 0 °C, 95%. (f) 9-BBN, THF, then NaOH, H\(_2\)O, 83% (1:1). (g) DM periodinane, CH\(_2\)Cl\(_2\), NaClO\(_2\), NaO\(_2\)PO\(_4\), 2-methyl-2-butene, (CH\(_3\))\(_2\)CO–THF–H\(_2\)O, 75% (two steps, 1:1). (h) NaIIO\(_4\), I\(_2\), CH\(_3\)CN, (C\(_6\)H\(_5\))\(_2\)SnH, (C\(_6\)H\(_5\))\(_2\)B, O\(_2\), C\(_6\)H\(_5\)CH\(_2\), THF, 0 °C, separation, 85% (two steps, 15a:15b, 1:1). (i) KOH, C\(_6\)H\(_5\)OH, 50% (66% combined yield of 15b). brsm = based on recovered starting material.

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\(4\) For leading references on recent applications of iron carbonyls in synthesis, see: Coquerel, Y. *Synlett* 2002, 1937–1938.
relatively high-field chemical shifts of H9 and H8 (5.97 and 6.06 ppm, respectively)\textsuperscript{10} and, in addition, by theoretical calculations.\textsuperscript{11}

Three exceptionally direct guaiane syntheses illustrate the effectiveness of this new methodology (Scheme 3). \(\alpha\)-Chloro-

5b was converted without double-bond migration or epimerization into its dimethyltrimethylene acetal, which smoothly gave \(\alpha\)-methylene-5b via its derivative 10a on halogen–metal exchange, methylation, and hydride oxidation (71%).\textsuperscript{12}

Regioselective oxymercuration of the exocyclic double bond of 10b, followed by selective hydrogenation of the nonconjugated double bond, afforded 1-epi-hydroxycolorenone (11), which on epimerization previously provided hydroxycolorenone (12)\textsuperscript{13} and on acetylation\textsuperscript{14} was found to give 8-desangeloyloxytorilin (13)\textsuperscript{15} in high yield. Acetal 10a also underwent regioselective hydroboration–oxidation to generate alcohols 14a (1:1, 83%), which could be efficiently oxidized in two steps with concomitant deprotection to carboxylic acids 14b. Iodolactonization of 14b, followed by deiodination, then stereoselectively afforded 11-epi-6-deoxygeigerin (15a) and 6-deoxygeigerin (15b)\textsuperscript{16} in 88% combined yield; the former could be converted to the latter with KOH. 6-Deoxygeigerin represents the first guai-9,12-olide to be prepared by total synthesis.

In summary, the easily secured hydroazulenone 3 undergoes numerous useful transformations with excellent regioand stereocontrol, as seen in part in the notably brief syntheses of hydroxycolorenone, 8-desangeloyloxytorilin, and 6-deoxygeigerin. The ubiquitousness of the bicyclo-[5.3.0]decane ring system in natural products should ensure broad use of 3 and its readily prepared analogues in synthesis. Current work is focused on the use of these compounds to access guai-6,12-olides and pseudoguaianolides,\textsuperscript{18} as well as the development of an asymmetric approach to the above chemistry.

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**Supporting Information Available:** Experimental procedure and characterization data for 3 and characterization data for 4, 5a, 5b, 6–8, 9a–c, 10b, 11, 13, and 15b. This material is available free of charge via the Internet at http://pubs.acs.org.


\textsuperscript{12} Chemical shifts of H6 and H7 are 6.84 and 6.41 ppm, respectively. Similar high-field H8,H9 chemical shifts and parallel regioselectivity were observed with analogues of 3.

\textsuperscript{13} B3LYP/6-31G* calculation of the coefficients of the frontier orbitals of 3 gives, respectively, for C7 and C9: LUMO 0.29 and 0.25, HOMO 0.20 and 0.22. The partial nonconjugated character of the C8,C9 double bond is also suggested by the calculated C7,C8–C9 dihedral angle (15.2 vs 2.3° for C4,C5–C6,C7).


\textsuperscript{16} Zdero, C.; Bohlmann, F. Phytochemistry 1989, 28, 3105–3120.


\textsuperscript{18} C-5 methyl conjugate addition to \(\alpha\)-chloro-

6-Deoxygeigerin represents the first guai-9,12-olide to be prepared by total synthesis.