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

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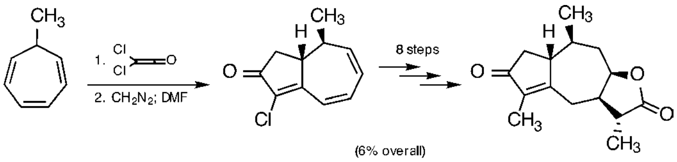
## ABSTRACT



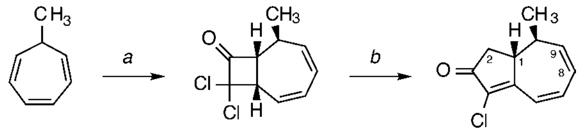
(±)-6-Deoxygeigerin

**A conceptually new and highly versatile approach to bicyclo[5.3.0]decanes, based on dichloroketene cycloaddition–diazoalkane 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 guanacastepenes).[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] (**1**, 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 diazomethane[5a] to afford, following dehydrochlorination,[5b] hydroazulenone **3** in 44% overall yield from **1** (76% yield per step).

**Scheme 1**[a]



**1** **2** **3**

[a] Reaction conditions: (a) $Cl_3CCOCl$, Zn−Cu, $POCl_3$, $(C_2H_5)_2O$. (b) $CH_2N_2$, $(C_2H_5)_2O-CH_3OH$; DMF, 44% overall (76% per step).

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(1) See: *Dictionary of Terpenoids*; Connolly, J. D.; Hill, R. A., Eds.; Chapman and Hall: New York, 1991. See also: Hanson, J. R. *Nat. Prod. Rep.* **2002**, *19*, 125−132. Fraga, B. M. *Nat. Prod. Rep.* **2002**, *19*, 650−672 and references therein.

(2) See: Heathcock, C. H.; Graham, S. L.; Pirrung, M. C.; Plavac, F.; White, C. T. In *The Total Synthesis of Natural Products*; ApSimon, J., Ed.; Wiley-Interscience: New York, 1983; Vol. 5. For some recent examples, see: Lee, K.; Cha, J. K. *J. Am. Chem. Soc.* **2001**, *123*, 5590−5591. Trost, B. M.; Shen, H. C. *Angew. Chem., Int. Ed.* **2001**, *40*, 2313−2316. Lin, S.; Dudley, G. B.; Tan, D. S.; Danishefsky, S. J. *Angew. Chem., Int. Ed.* **2002**, *41*, 2188-2191. Kumar, J. S. R.; O'Sullivan, M. F.; Reisman, S. E.; Hulford, C. A.; Ovaska, T. V. *Tetrahedron Lett.* **2002**, *43*, 1939−1941. Winkler, J. D.; Rouse, M. B.; Greaney, M. F.; Harrison, S. J.; Jeon, Y. T. *J. Am. Chem. Soc.* **2002**, *124*, 9726−9728, and references therein.

(3) Günther, H.; Görlitz, M.; Hinrichs, H. H. *Tetrahedron* **1968**, *24*, 5665−5676. Tropylium tetrafluoroborate is now commercially available.

(4) Coquerel, Y.; Blanc, A.; Deprés, J.-P.; Greene, A. E.; Averbuch-Pouchot, M.-T.; Philouze, C.; Durif, A. *Acta Crystallogr.* **2000**, *C56*, 1480−1481. For an application, see: Yokoyama, R.; Ito, S.; Watanabe, M.; Harada, N.; Kabuto, C.; Morita, N. *J. Chem. Soc., Perkin Trans. 1* **2001**, 2257−2261.

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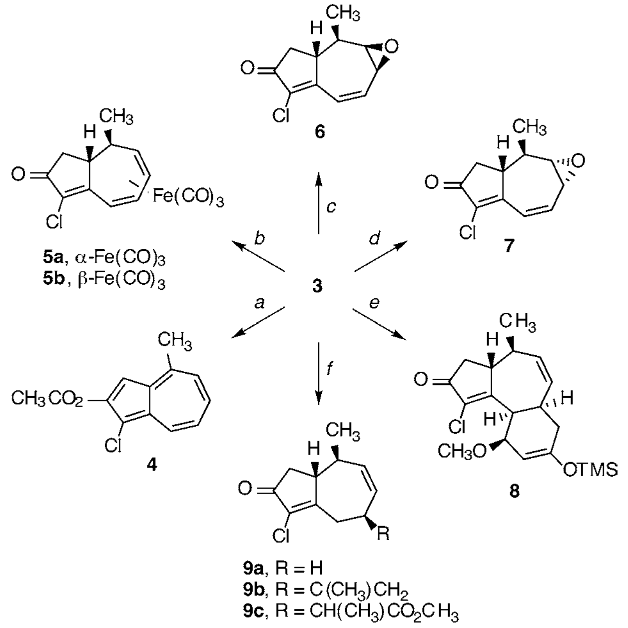
Significantly, other cycloheptatrienes[3] (e.g., H, *i*-$C_3H_7$, $C_6H_5$ replace $CH_3$ in **1**) and other diazoalkanes (e.g., $CH_3CHN_2$[6]) have also been used in this sequence and with comparable efficiency.

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 α-chloro-cyclopentenone portion of **3**, the tricarbonyliron complexes **5** can be readily generated through treatment with $Fe_2(CO)_9$ (**5a**:**5b**[7] = 2.3:1).[8] Further possibilities arise from the highly selective and efficient epoxidations that can be achieved at the distal unsaturation in **3**: *m*-CPBA gives the β-epoxide **6**[7] (dr = 9:1), while NBS−LiH produces in good yield the α-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, rhamnofolanes, sphaeroanes, and tiglianes.

**Scheme 2**[a]

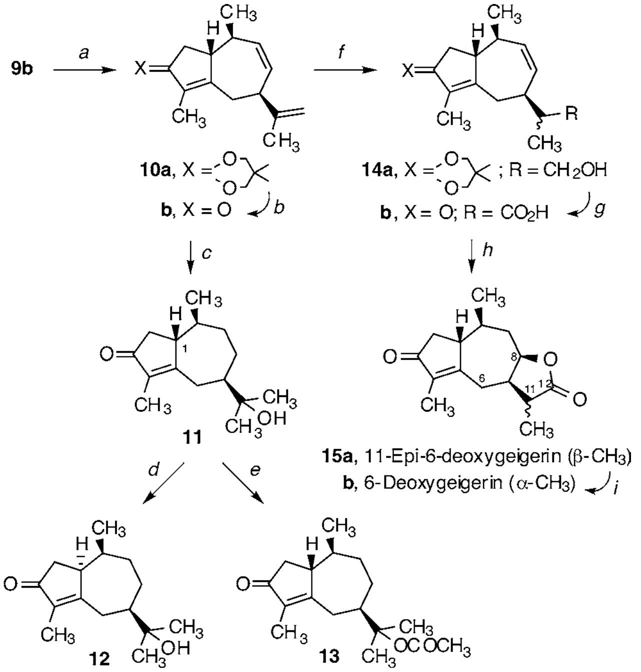


[a] Reaction conditions: (a) Pd/C, $(CH_3CO)_2O$, $C_6H_5CH_3$, 120 °C, 50%. (b) $Fe_2(CO)_9$, $(C_2H_5)_2O$, reflux, 76% (93% brsm). (c) *m*-CPBA, $CH_2Cl_2$, 97%. (d) NBS, THF−$H_2O$; LiH, DMF, 79% (two steps). (e) $CH_2{=}C(OTMS)CH{=}CH(OCH_3)$, $C_6H_5CH_3$, 180 °C, 31%. (f) **9a**: K-Selectride, THF-DMPU, −80 to −40 °C, 67%. **9b**: $BrMgC(CH_3){=}CH_2$, CuBr·DMS, TMSCl, THF, −80 °C, 45% (dr ≥ 10:1). **9c**: $CH_3CH{=}C(OTBDMS)(OCH_3)$, $LiClO_4$, $CH_2Cl_2$, 79% (dr = 6:1). brsm = based on recovered starting material.

Finally, and perhaps most importantly, *conjugate addition to trienone **3** proceeds with remarkable stereo- and regioselectivity to yield the β 1,6 adducts.* For example, conjugate addition with K-Selectride, isopropenylmagnesium bromide, and the *tert*-butyldimethylsilyl ketene acetal from methyl propionate[9] selectively provides adducts **9a**−**c**,[7] respectively. The C-7-substituted unsaturated adducts **9b**,**c** 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

**Scheme 3**[a]



[a] Reaction conditions: (a) $(HOCH_2)_2C(CH_3)_2$, $(CH_3O)_3CH$, TsOH, MS, $CH_2Cl_2$, 76% (90% brsm); *N*,*N*-dimethyl-1-naphthylamine, Li, THF, −80 °C, then $CH_3I$, −80 to 20 °C, 93%. (b) 10% HCl, THF, quant. (c) $Hg(OCOCF_3)_2$, THF−$H_2O$, then NaOH, $NaBH_4$; $H_2$, Pd/C, $CH_3CO_2C_2H_5$, 55% (two steps). (d) KOH, $CH_3OH$, 46% (92% brsm).[13a] (e) $(CH_3CO)_2O$, $CF_3SO_3TMS$, $CH_2Cl_2$, 0 °C, 95%. (f) 9-BBN, THF, then NaOH, $H_2O_2$, 83% (1:1). (g) DM periodinane, $CH_2Cl_2$; $NaClO_2$, $NaH_2PO_4$, 2-methyl-2-butene, $(CH_3)_3COH$-THF−$H_2O$, 75% (two steps, 1:1). (h) $NaHCO_3$, $I_2$, $CH_3CN$; $(C_4H_9)_3SnH$, $(C_2H_5)_3B$, $O_2$, $C_6H_5CH_3$–THF, 0 °C; separation, 88% (two steps, **15a**:**15b**, 1:1). (i) KOH, $C_2H_5OH$, 50% (66% combined yield of **15b**). brsm = based on recovered starting material.

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(5) (a) Greene, A. E.; Deprés, J.-P. *J. Am. Chem. Soc.* **1979**, *101*, 4003−4005. (b) Deprés, J.-P.; Greene, A. E. *J. Org. Chem.* **1980**, *45*, 2036−2037.

(6) Marshall, J. A.; Partridge, J. J. *J. Org. Chem.* **1968**, *33*, 4090−4097. The use of diazoethane with the cycloheptatriene cycloadduct leads stereoselectively to the β-methyl trienone derivative (NOE).

(7) Structure and stereochemistry of **5b**, **6**, and **9b** were determined by X-ray diffraction analysis. Crystallographic information files (CIF) for **5b**, **6**, and **9b** have been deposited at the Cambridge Crystallographic Data Centre and can be obtained online free of charge (or upon request from the Cambridge Crystallographic Data Centre, 12, Union Road, Cambridge CB2 1EZ, UK. Fax: (+44) 1223-336-033. E-mail: deposit@ccdc.cam.ac.uk).

(8) 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)[10] and, in addition, by theoretical calculations.[11]

Three exceptionally direct guaiane syntheses illustrate the effectiveness of this new methodology (Scheme 3). α-Chloroenone **9b** was converted without double-bond migration or epimerization into its dimethyltrimethylene acetal, which smoothly gave α-methylenone **10b** via its derivative **10a** on halogen−metal exchange, methylation, and hydrolysis (71%).[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**)[13] and on acetylation[14] was found to give 8-desangeloyloxytorilin (**13**)[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**)[16] in 88% combined yield; the former could be converted to the latter with KOH.[17] *6-Deoxygeigerin represents the first guaian-8,12-olide to be prepared by total synthesis.*

In summary, the easily secured hydroazulenone **3** undergoes numerous useful transformations with excellent regio- and 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 guaian-6,12-olides and pseudoguaianolides,[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.

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[9] Wilcox, C. S.; Babston, R. E. *J. Org. Chem.* **1984**, *49*, 1451−1453. Reetz, M. T.; Fox, D. N. A. *Tetrahedron Lett.* **1993**, *34*, 1119−1122.

[10] 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**.

[11] 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 C6,C7−C8,C9 dihedral angle (15.2 vs 2.3° for C4,C5−C6,C7).

[12] Guaciaro, M. A.; Wovkulich, P. M.; Smith, A. B., III. *Tetrahedron Lett.* **1978**, 4661−4664. Bachki, A.; Foubelo, F.; Yus, M. *Tetrahedron* **1997**, *53*, 4921−4934.

[13] (a) Ishii, H.; Tozyo, T.; Nakamura, M.; Minato, H. *Tetrahedron* **1970**, *26*, 2751−2757. (b) From natural sources: Jakupovic, J.; Pathak, V. P.; Grenz, M.; Banerjee, S.; Wolfrum, C.; Baruah, R. N.; Bohlmann, F. *Phytochemistry* **1987**, *26*, 1049−1052. Handayani, D.; Edrada, R. A.; Proksch, P.; Wray, V.; Witte, L.; van Ofwegen, L.; Kunzmann, A. *J. Nat. Prod.* **1997**, *60*, 716−718. Labbé, C.; Faini, F.; Coll, J.; Carbonell, P. *Phytochemistry* **1998**, *49*, 793−795.

[14] Procopiou, P. A.; Baugh, S. P. D.; Flack, S. S.; Inglis, G. G. A. *J. Org. Chem.* **1998**, *63*, 2342−2347.

[15] Ryu, J.-H.; Jeong, Y. S. *Arch. Pharm. Res.* **2001**, *24*, 532−535.

[16] Zdero, C.; Bohlmann, F. *Phytochemistry* **1989**, *28*, 3105−3120.

[17] Barton, D. H. R.; Pinhey, J. T.; Wells, R. J. *J. Chem. Soc.* **1964**, 2518−2526.

[18] C-5 methyl conjugate addition to α-chloroenone **9b** can be achieved stereoselectively in the required sense and in good yield with $CH_3Cu{\cdot}BF_3$ to give an advanced pseudoguaianolide precursor.